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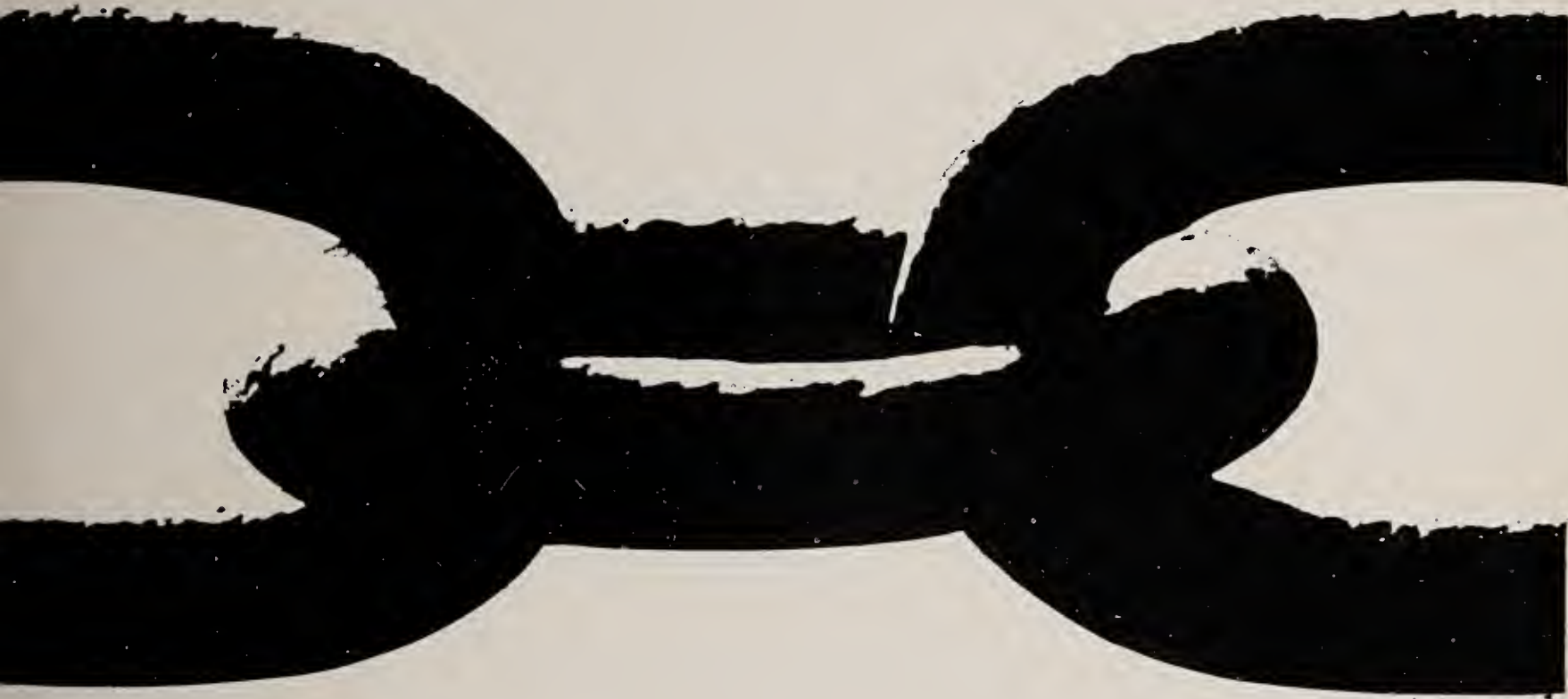
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Editorial:

On The Oncoming Obsolescence Of Orthodox Obstetrics

In the last few years there has been much discussion concerning the possible socio-economic sequelae of the oral contraceptive pill; but on the whole one gathers that this discussion has been taken none too seriously by physicians, because of the long time that most of the sequelae would take to manifest themselves. Evidence is now accumulating that Canada is now beginning to feel rather serious social effects from the mass usage of contraceptive pills. The Financial Post reported last year that manufacturers of baby apparel and baby products such as canned foods and carriages were indeed beginning to cut down production and that some were contemplating the possible necessity of mergers because of the high volume low profit per unit nature of their business.

Those concerned with hospital planning and administration are right now querying what to do about the decreasing births and increasing maternity-bed vacancies in their hospitals. Although the situation is somewhat masked in the major teaching hospitals because of continued influx of immigrants, one only has to talk to administrators in "Elsewhere General" to become convinced of the scope of the problem that exists today. In the Brampton-Bramalea area, births per month have come down from approximately 120 to 95 in 3 years, and yet the local population has increased from 25,000 to 45,000 in the same period. In Picton, a stable community of 5200, the births per month have decreased some 20% over 3 years. In fact, one of the doctors in Picton told me recently that some thought in the near future may be given to changing at least 50% of their maternity wing into medical or surgical beds. Whether the decreasing birth rate means couples are merely postponing their pregnancies or whether the trend to limit family size is real we cannot yet say.

Notwithstanding the serious import of these socio-economic sequelae and not wishing to get into that mare's nest of future moral patterns, I would like to cast a glance at what some bright souls have termed "The Planned Obsolescence of the Obstetrician". Perhaps it is too radical to suggest that the obstetrician in Canada may become obsolete, but one only has to look to the smaller Ontario centres today to find an increasing number of obstetricians doing what is loosely termed an obstetrical general practice whereas 5 years ago obstetricians in the smaller centres could find an adequate amount of work to do on a referral basis only. If this trend continues, it is a matter of conjecture whether men and women will want to spend an extra 4-5 years in training just to do an obstetrical general practice. Of course the alternatives of research or a purely gynecologic practice are still open and in fact are expanding rapidly.

The nastiest blow may be yet to come: test-tube babies. Work in this field underwent a glare of publicity several years ago in Italy when the Pope publicly intervened to ask a researcher to suspend his studies. However, somewhere, in some laboratory, you can be sure that there is bubbling a test-tube pregnant with ill tidings for obstetricians. With a slight stretch of the imagination, one can see George Orwell's medical student watching an old and venerable doctor walk down the now musty aged corridors of 4CB Toronto General Hospital; and then turning to his companion say, "Would you believe an obstetrician?"

A.B.D.

I wish to express my sincere thanks to Dr. Paul for writing in the Journal. He has indicated a plethora of future research problems in the broad field of Obstetrics and Gynecology. This Journal has tried to concern itself with the fascinating subject of hormones as they relate to this specialty. I particularly wish to direct the reader's attention to J. Branson's article on postmenopausal estrogen therapy in view of the increasing importance and public distortions of this subject in the popular press.

I undertook the editorship of this particular Journal issue on the understanding from the editors-in-chief that the main purpose of the Journal would be to encourage students who had never written an article for a medical publication before. I am sure that as you read through the various articles, you will agree with me that the contributors have achieved a clear and concise flow of ideas. If this Journal serves only to encourage those students in succeeding years who have never before written a scientific article, then, in my opinion it will have achieved its main purpose.

A.B.D.

Guest Editorial

WILLIAM M. PAUL is Gordon C. Leitch Professor and Head of the Department of Obstetrics and Gynaecology, and Obstetrician and Gynaecologist-in-Chief to the Toronto General Hospital. A Toronto graduate, he was Resident in Toronto's Western and General Hospitals, and also trained in the Department of Embryology, Carnegie Foundation, Baltimore. He was Director of Obstetrics and Gynaecology, University of Alberta, 1962-65. Dr. Paul's research interests principally involve studies of fetal cardiovascular regulation.



Your editor was kind enough to allow me to glance at some of the contributions to this issue prior to going to press, and I was once again reminded how rapidly the field of obstetrics and gynaecology has changed and hopefully how rapidly our horizons may continue to widen. Originally a wedding between surgery and midwifery and largely involved in the surgical problems of the pelvis or the mechanical problems of labour, obstetrics and gynaecology is now concerned with the entire reproductive process and the reproductive apparatus.

The recent introduction of oral progestational steroids revolutionized the treatment of functional uterine bleeding, but their use in contraception has touched off one of the liveliest medical, social, ethical and religious debates of our time. An increased insight into the factors involved in ovulation and our subsequent ability to influence them is an example, I think, of how a search for mechanisms rather than for mechanics yields the real dividends of progress.

Childbearing can be said now to be a safe process—for the mother. But a glance at our reproductive failures quickly indicates that the same does not hold true for the fetus. Aside from a 10% loss by abortion, we still accept a high fetal loss from prematurity, malformation and other complications. A search for the mechanism behind reproductive failure encompasses a very wide range of enquiry—from genetics and cellular biology to the characteristics of flow through the intervillous space. The gaps in our knowledge of such mechanisms are immense. The morphology of nidation is well described, but how much do we know about the process itself? How many pages in our text books of physiology are devoted to the fetus, or the mechanisms of uterine action, or placental blood flow? How much information do we have about the immunologic implication of a successful placental implantation? Reproductive failure will only be understood when the basic mechanisms involved in the reproductive process are understood.

At the risk of being accused of using your editorial page as a recruiting stand, I would suggest that study of reproduction, and its clinical arm, obstetrics and gynaecology, is going to provide an exciting and rapidly developing area of activity. I'm looking forward to it!

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Oral Contraceptives

P. V. Clarke 6T7

I THE NORMAL MENSTRUAL CYCLE

(i) Follicular Phase (estrogenic or proliferative phase)

Immediately following menstruation, the endometrium is denuded down to the basilar layer, and blood estrogen and progesterone levels are at their lowest. Low blood estrogen level serves to trigger the hypothalamus to secrete FSH releasing factor which subsequently leads to the release of FSH by the pituitary. The Graafian follicle which is to mature begins to enlarge under the influence of FSH. The follicle proliferates, and the theca interna begins to produce estrogen. The effect of estrogen on the endometrium is initially reparative and later proliferative. Columnar epithelium grows over the raw surface from the glandular crypts; the stroma and glands enlarge, and the spiral arteries from the basalis grow into the newly developing endometrium and become coiled.

(ii) Ovulation

Approximately fourteen days prior to menstruation, ovulation takes place. When estrogen blood levels reach a critical point, LH releasing factor is secreted by the hypothalamus, and the pituitary releases LH. FSH together with LH cause a rupture of the follicle and discharge of the ovum into the peritoneal cavity.

(iii) Secretory Phase (luteal or progestational phase)

Following ovulation, the follicle undergoes lutenization under the influence of LH. The granulosa cells proliferate and some of the thecal cells proliferate to form the theca lutein cells. The former secrete mainly progesterone under the action of LTH while the latter continue to secrete a little estrogen. The actual trigger mechanism for the release of LTH is unknown although a releasing factor is believed to be involved. A rising level of blood progesterone inhibits further release of LH by the pituitary. The endometrium, under the influence of progesterone, begins to secrete glycogen, and the glands become tortuous and ragged in appearance. As blood levels of progesterone continue to rise, the release of LTH is suppressed. Estrogen metabolites are also believed to play a role in LTH suppression. When LTH secretion is suppressed, the corpus luteum fails, and progesterone and estrogen are no longer produced. Blood levels of these hormones fall, and the spiral arteries of the endometrium go into alternate periods of spasm and relaxation producing periods of endometrial ischemia.

(iv) Menstrual Phase

During the periods of ischemia, necrosis of the decidual endometrium occurs, causing it to slough. During the periods of relaxation of the arteries, hemorrhage occurs, and the necrotic debris, together with the blood are discharged through the cervix into the vagina. About

fifty to a hundred and fifty cubic centimeters of blood are lost each period. This phase may last three to seven days, the average being five.

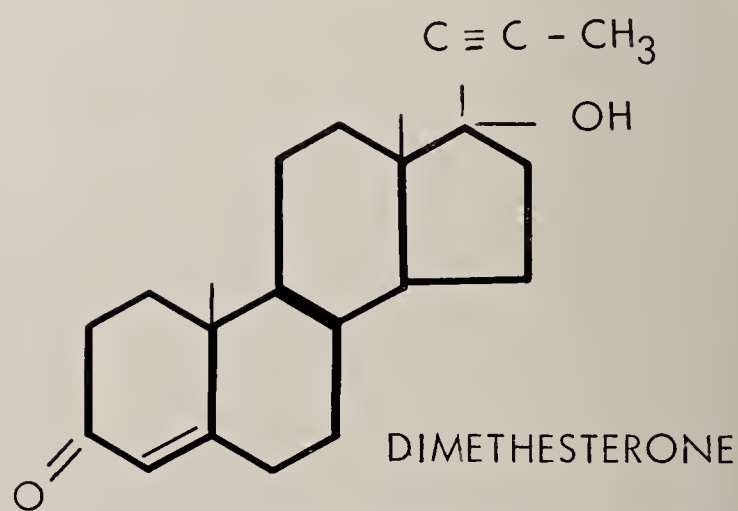
II HISTORY OF ORAL CONTRACEPTION

Early in this century, it was realized that the corpus luteum could inhibit ovulation. In 1934, progesterone was isolated, and in 1937, Makepiece et. al.¹ showed that it could prevent ovulation. It was also discovered that testosterone and estrogen could inhibit ovulation, but were deemed undesirable clinically because of their side effects. In 1954, Djerassi² showed that steroids could be synthesized, and that some of these synthetics had progestational activity. In 1958, Pincus³ surveyed this field of synthetic progesterones and found that three of them were very potent ovulation inhibitors. These were norethisterone, ethynortestosterone, and norethynodrel. In 1957, Rock et. al.⁴ while treating infertility with estrogen and progesterone discovered that amenorrhea was a side effect. (They were using continuous long term administration). Realizing that ovulation had been prevented, they devised an experiment to test three potent steroids as contraceptive agents. The results of this classical experiment were published in 1957, and using endometrial and vaginal changes and, occasionally ovarian biopsy at laparotomy as criteria, they discovered in most cases that ovulation had been inhibited by this treatment, and that these were in fact preventing conception. As a result of these and animal tests, norethynodrel (Enovid[®]) in a ten milligram dose was chosen for a pilot study in contraception, carried out in Puerto Rico in April 1956 under Pincus and Rice-Wray.

III CHEMISTRY

The oral synthetic progestational agents in use presently may be divided into four chemical classes for the purposes of study:

Group 1 — Testosterone Derivatives



Dimethyl ethisterone (dimethisterone) was the first orally-active progestational agent synthesized. While it has been used clinically for over twenty years, it is not a very active product.

ORAL CONTRACEPTIVES

FIG. 1.: The normal menstrual cycle.

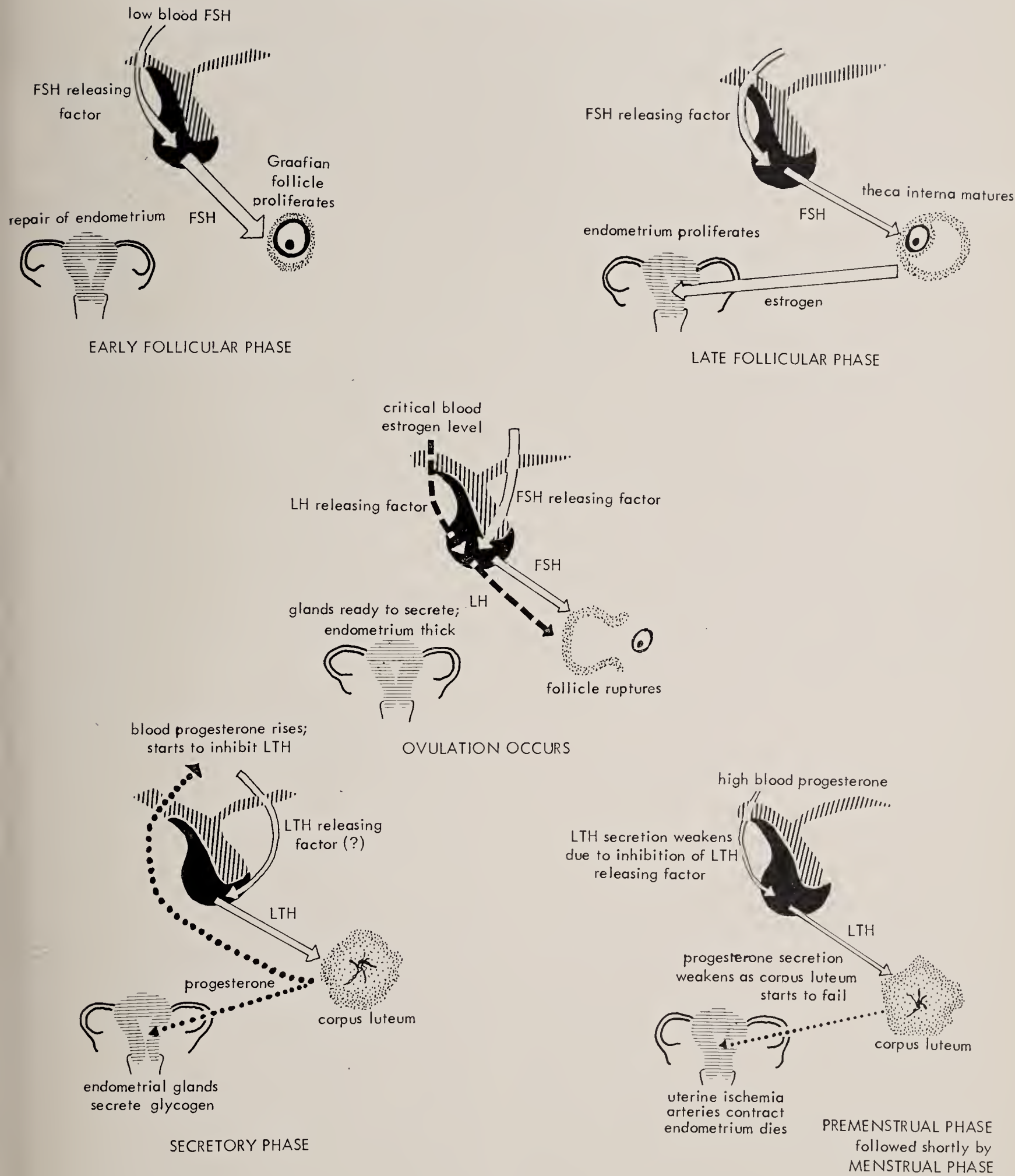
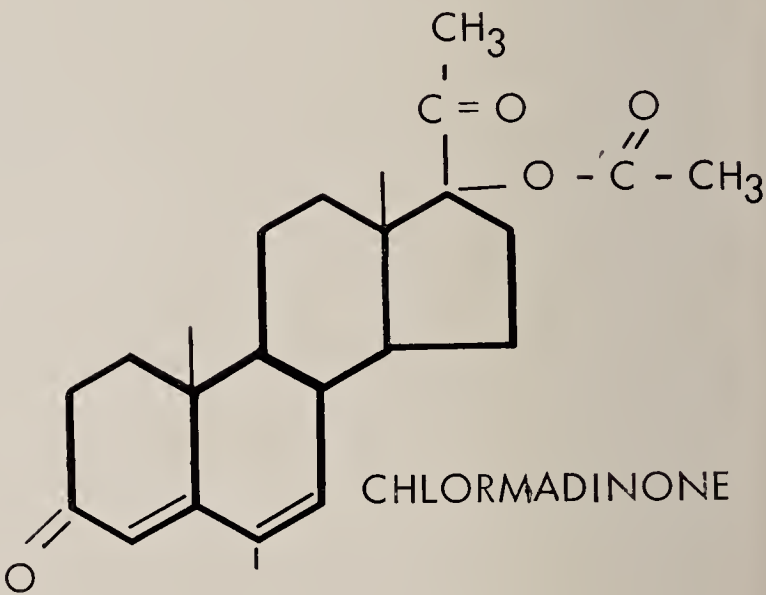
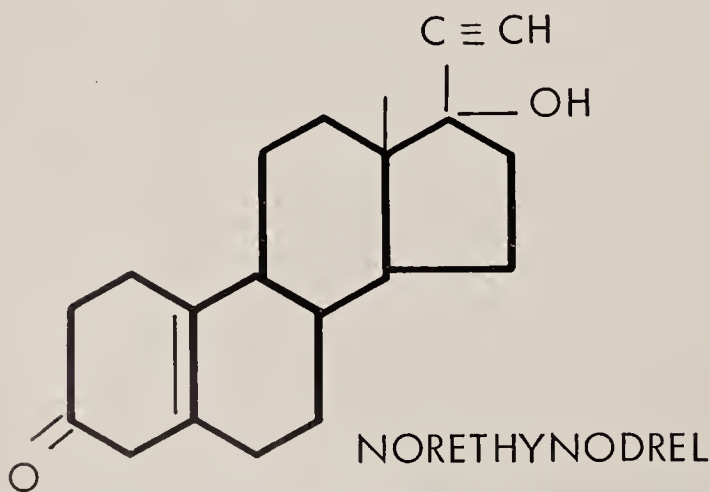
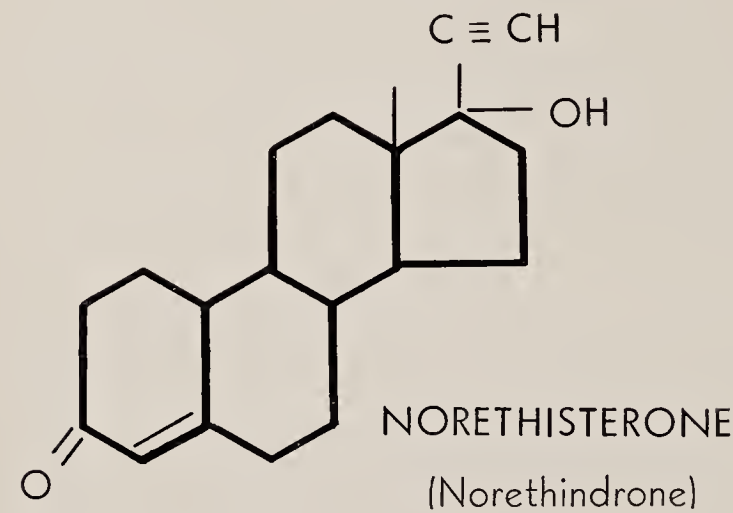


TABLE I: AVAILABLE ORAL CONTRACEPTIVES

Name	Progestogen	Dose	Estrogen	Dose
Enovid	chlormadinone	2 mg	mestranol (ethinylestradiol 3-methyl ether)	0.15 mg
Enovid-E	norethynodrel	9.85 mg	mestranol	0.1 mg
Norinyl	norethindrone	2 mg	mestranol	1.0 mg
Norlestrin	norethindrone	2 mg	ethinylestradiol	0.05 mg
Oracon	dimethesterone	25 mg	ethinylestradiol	0.1 mg
OrthoNovum I	norethindrone	1 mg	mestranol	0.05 mg
OrthoNovum II	norethindrone	2 mg	mestranol	0.1 mg
OrthoNovum V	norethindrone	5 mg	mestranol	0.075 mg
Ovulen	ethynodiol diacetate	1 mg	mestranol	0.1 mg

Group 2 — 19-Nortestosterone Derivatives

Group 3 — 17-Alpha-Hydroxyprogesterone Derivatives



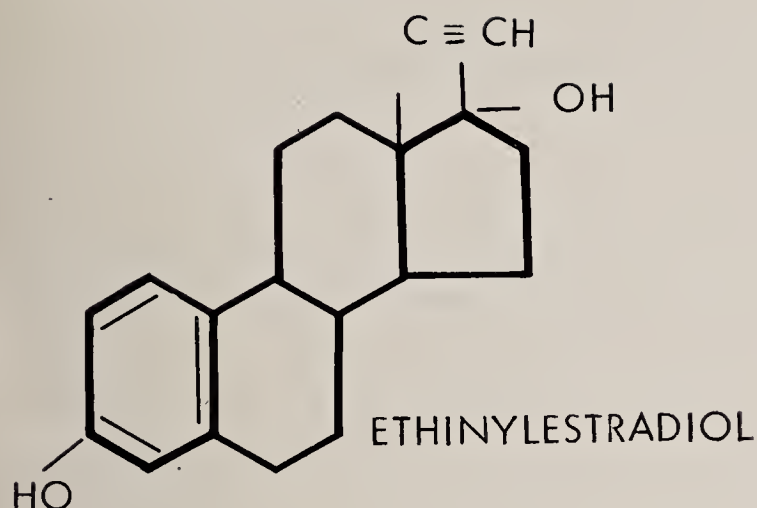
In these compounds, the OH at carbon 17 must be eliminated by esterification before a progestationally active substance is available. This is a more variable group and the clinical characteristics depend upon what other moieties are added to the molecule. They are less powerful ovulation inhibitors than those in group 2, but some are more powerful progestogens, giving increased endometrial secretory changes. They are less hemostatic, and have no inherent estrogenicity.

Group 4 — Progesterone Derivatives

These do not inhibit ovulation, give poor cycle control, and are not metabolized to estrogen. They are not helpful in controlling uterine bleeding, but are helpful in the treatment of dysmenorrhea.

There are the most powerful ovulation inhibitors. They have the most hemostatic effect on uterine bleeding of endocrine origin. They produce a normal secretory response in estrogen-primed endometrium, and administered orally cyclically, cause a decreased menstrual blood loss. Compounds of this group also have some estrogenic activity (especially norethynodrel), as they are metabolized to estrogens.

The Addition of Estrogens



When estrogen-progesterone tablets are given early in the cycle, as they are when they are used as oral contraceptives, there is a suppression of endogenous estrogen and progesterone excretion. Theoretically, group 2 progestogens could be used alone. Those with no estrogen activity require the addition of estrogen to support the endometrium thereby preventing breakthrough bleeding and giving better control of the cycle. The dose of progestogen can be reduced when estrogen is included, and since progestogens are more expensive than estrogens, the cost can be reduced while maintaining the efficiency of the product.

IV MODE OF ACTION

It is generally agreed that these drugs work by preventing ovulation as discussed above. They may do this in one of two ways:

1) by suppressing the gonadotropin (FSH, LH, LTH) of the pituitary. This probably works via the hypothalamus in the nature of a feedback system. As evidence, estrogen has been shown to prevent ovulation if given early enough in the cycle. It is inferred that it therefore inhibits the release of FSH. Progestational compounds may block the output of LH so that FSH and LH do not reach the critical level necessary to produce ovulation.

2) by a direct action upon the ovary. Although the literature gives conflicting evidence, the majority of animal experiments (not that these issues should be settled by a popular vote) make this an unlikely possibility. In animals, gonadophysin administered to animals normally causes an increase in ovarian weight. The subsequent administration of norethindrone does not block this effect. In humans 100 mg of progesterone given to patients receiving FSH has been shown by some experimenters to cause a decrease in the effect of FSH. This they claim may be due to a direct effect upon the ovary. However, the assay methods they used for measurement of FSH have been held to doubt, and more recent experimenters have been unable to confirm their findings using better assay techniques.

It seems likely therefore that in the light of the evidence presently available these steroids act indirectly on the pituitary, via the hypothalamus, to prevent the release of gonadotropins.

These products also suppress the release of endogenous estrogen and progesterone if administered early enough in the cycle. They also alter the endometrium histologically and may prevent implantation. They may in addition change the consistency of the cervical mucus, rendering it hostile to spermatozoa.

These pills are administered for twenty consecutive days beginning on the fifth day after the onset of menstrual bleeding. Most women experience a lighter amount of menstrual bleeding from three to four days after stopping the pills. The products available on the market today are as near as possible to one hundred percent effective. Reduction in efficacy can be expected in women who take the tablets sporadically or who miss even one tablet. The occurrence of pregnancy with this latter happening is fortunately rare, even on the new low dose preparations. The overall success rate in several hundred thousand cycles tested is in the range of ninety-nine and three quarters per cent.

V INDICATIONS AND CONTRAINDICATIONS

1) Indications

a) *contraception*: These tablets provide safe, relatively cheap, very effective contraception. Unlike other means of contraception such as diaphragms, condoms, creams, etc., which of necessity make the sex act premeditated, these products give considerably more freedom.

b) *severe dysmenorrhea and some dysfunctional uterine bleeding*

c) *oligomenorrhea*: these agents may be used to regulate irregular or infrequent periods.

d) *menorrhagia*: women on 'the pill' generally experience a decreased amount of menstrual flow.

2) Contraindications

a) *uterine fibroids*: leiomyomata tend to increase in size in patients receiving oral contraceptives.

b) *thrombophlebitis*: while the evidence linking this condition with 'the pill' is tenuous, it is still felt among most clinicians that women with a predisposition to this disorder should not receive oral estrogens, or at least while they have the disease.

VI POSSIBLE SIDE EFFECTS

It should be stated at the outset that every conceivable symptom has been linked by women on these drugs and even by some physicians to oral contraceptive agents. Now that these drugs have been with us for some years, most of these symptoms have been dis-

pelled, and a great many have been attributed to fantasy and neurosis. Many women when they first start taking oral contraceptives experience a *weight gain* of a couple of pounds. This may possibly be due to the inherent salt-retaining nature of all steroid drugs. Excessive gain in weight however cannot be blamed on the pill. At the onset of therapy, some women also experience a little *nausea*. This is probably due to the estrogen in the tablet. (Women in their first trimester of pregnancy also experience nausea — this has also been attributed to high blood estrogen levels.) Acclimatization to this side effect occurs in a few days in most women.

Thus far, there has been no reason to suspect that long term administration of these drugs has any untoward sequelae. There have been no effects on the pituitary observed, nor has fertility been decreased on stopping the drug. In fact many clinicians will prescribe these drugs for a few cycles in their infertile patients, believing that on cessation, their fertility will be increased. It is pretty well agreed that continuous long term estrogen therapy produces a hypertrophied and even hyperplastic endometrium that in some cases is premalignant; however in cyclic estrogen therapy, no such changes have been found. Moreover, the progestogen found in contraceptives offers a protective effect against carcinoma of the endometrium.

VII SEQUENTIAL THERAPY

The discovery that the 19-nortestosterone derivatives themselves are metabolized to estrogens raised the question that estrogens alone could be used to inhibit ovulation, since they themselves are known to inhibit pituitary gonadotrophins. As early as 1947, Goldzieher et al.⁵ showed that mestranol by itself is capable of inhibiting ovulation for at least twelve consecutive cycles. Unlike other estrogens used previously, mestranol does not allow 'pituitary escape' and ovulation. Hence a new concept of a more physiological control of contraception has evolved consisting of the administration of mestranol for twenty consecutive days per month, supplementing the final five days of treatment with a potent progestational agent such as chlormadinone (Lormin, Eli Lilly; C-Quens, Eli Lilly; SQ's, Ortho), to produce satisfactory endometrial maturation and to ensure regular and consistent withdrawal bleeding. Reports of the efficiency of this type of drug compare favourably with the older form of cyclic therapy.

VIII SUMMARY

The above represents a review of the topic of oral contraception, its principles, history, chemistry, mode of action, indications and contra-indications, and results of their use. The author wishes to underline in closing that for our present society, these agents represent the contraceptive method of choice for most patients. Their discovery and implementation represents one of the foremost medical and sociological triumphs in the last fifty years.

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Postmenopausal Estrogen Therapy

J. Branson 6T7

INTRODUCTION

The long-term use of estrogens in the treatment of menopausal and postmenopausal females poses a major problem for the practising physician. These agents have been the subject of medical controversy for many years, and the literature is contradictory and confusing. The pharmaceutical companies have contributed to the problem by massive advertising campaigns aimed principally at the doctor. These campaigns are made more understandable if one considers that there are twenty-five million postmenopausal women in Canada and the United States alone. The estimated cost of total estrogen replacement would be fifty dollars per woman per year, a potential sales volume of one and one quarter billion dollars. Female patients are also vitally interested in this treatment. The many articles in the popular press have promised them everything from the elimination of the menopause to a veritable fountain of youth. To a woman who is about to lose her "femininity", these promises are very attractive.

Thus, the physician is being put under considerable pressure to use estrogen replacement therapy, and yet he has little accurate and unbiased information upon which to base his treatment. The purpose of this article is to review and evaluate the present concepts in this field, in the hope of clarifying some of the confusion.

The menopause marks the end of the reproductive life of the female. Her ovaries cease to release ova and, more importantly, cease to secrete estrogens and progesterone. This relatively sudden fall in gonadal hormone production, in some women, has no physiological parallel in the male where the testicular function diminishes slowly. Thus, it may be logical to re-establish the "normal" hormone balance if the replacement is shown to have a beneficial effect, and if side effects do not outweigh the benefits achieved. Many physicians have argued that the menopause is "Nature's way" and that the medical profession has no right to tamper with the normal aging process. Workers who support the use of therapy reply that the development of presbyopia is also "Nature's way", yet no physician would deny a patient corrective lenses simply because gradual loss of visual activity was part of the normal aging process.

This group also points out that the life expectancy of a woman today is seventy-five years, compared to fifty years at the turn of the century; thus, modern medical practice has sentenced women to spend a third of their lifetime in an essentially castrated state.

Dr. Richard Wilson¹ sums up the view held by the majority of endocrinologists today — "The time for

philosophic debate is now over and it is imperative that the relationship of the menopausal symptom-complex to the deficiency of gonadal steroids be assessed objectively and studied scientifically." Objective research must demonstrate the efficacy of estrogen replacement and produce a practical means of administering this therapy.

CARCINOGENIC EFFECT

One of the most formidable deterrents to estrogen supplementation has been the fear that these hormones are carcinogenic. Textbooks of gynaecology, published as recently as 1965, cite an incidence of endometrial carcinoma as high as twenty percent in women with granulosa cell tumors of the ovary²—a tumor which usually secretes estrogens. Other workers have postulated a carcinogenic effect in other malignancies of the female reproductive tract and breast.

Certainly unopposed estrogens cause endometrial hyperplasia, but whether these agents cause malignancy or even stimulate a pre-malignant growth is open to serious question. Clinical trials seem to suggest otherwise. G. S. Gordon³ conducted a study from 1947 to 1957, using as subjects one hundred and twenty osteoporotic patients who were being treated cyclically with estrogens. His results summarized in Table I show no increased incidence of neoplasms, and even suggest that there may be some protective function against malignancy with this therapy. These results have been verified by a number of other workers.

TABLE ONE — NEOPLASMS DETECTED
(Estrogen-treated osteoporotic women 1947-1957)

Number of patients in study (Semiannual physical examination, gynecologic consultation, cytologic examination of vaginal smear)	120
Malignant neoplasms predicted	5
Neoplasms found:	
Adenomatous hyperplasia of endometrium	2
Adenomyosis uteri	1
Fibroadenoma of breast	1
Parathyroid adenoma	1
Malignant tumor	0

Previous experimental evidence did support the view that estrogens were carcinogenic. However, the evidence was based on the earlier development of malignancy in cancer-prone strains of mice after they had been given massive doses of estrogens. The application of these findings to the use of much lower doses in normal human females has been questioned, but the animal experiments have suggested that estrogens are contraindi-

cated in "cancer-prone" women. Thus, most authorities do not advocate the use of these agents in patients who have cancer of the ovary, endometrium, or estrogen-related breast tumors.

Similarly, in non-malignant estrogen-dependent diseases such as endometriosis, unopposed estrogens are also contraindicated; however, with these exceptions, the danger of stimulating malignancy is not a barrier to the long-term use of estrogens.

OSTEOPOROSIS

Osteoporosis is a major orthopedic disorder in twenty-six per cent of all women past the age of 60. The symptoms of this disease vary from pain in the lumbar spine to fracture of the hip, wrist, shoulder and vertebrae. Vertebral fractures lead to kyphosis and loss of stature. Although this condition is usually associated with bone pain, many patients with marked radiographical evidence of the disease have no discomfort.

The term osteoporosis signifies simply too little bone. Radiological examination shows thinning of the cortex, while pathological studies demonstrate thinning of the trabeculae. Workers⁴ using strontium tracers have shown that these patients have a small mineral pool, subnormal turnover of osteoid tissue, and decreased bone deposition. It has been suggested that this process is normal with aging, and that the condition as found in post-menopausal patients represents a pathological end-point of a physiologic process.

Since the work of Albright⁵ in the 1940's, it has been postulated that lack of estrogen played an important role in the etiology of post-menopausal osteoporosis. The level of gonadal hormones falls more rapidly and completely than in their male counterparts and, thus, women are much more susceptible to this disease. Even more convincing is the fact that women who have been surgically castrated develop osteoporosis in as little as three years, as compared to normal women in whom its postmenopausal onset is rarely seen before ten years. The investigation of this degenerative process is hampered by the lack of an accurate parameter. Many investigators have used the radiographic density of a particular bone at a specific site to evaluate treatment programs. More sophisticated techniques have been evolved using radioactive sources, but these also rely on densitometry. Whether densitometry can actually measure changes in the disease process has not been definitely established.

Some workers have correlated the progression of the disease with loss of stature, stating that this method is more sensitive, as the total osteoporotic changes in all the vertebrae are measured. With these techniques, soft tissue changes also enter into the results. Perhaps a better method is one in which the rate of bone deposi-

tion and turnover can be accurately assessed. Unfortunately, bone metabolism is affected by a number of factors which are difficult to control—dietary intake of calcium and other minerals, steroid hormone balance and the patient's level of activity to name a few. Again, the situation exists where measurements are being made, but no one can be sure what is being measured.

If one considers these studies, the results are impressive even when their limitations are taken into account. Wallach and Henneman⁶ followed twenty-seven patients who received estrogen therapy for periods ranging from five to twenty-five years. The patient's loss of height was used as the index of the osteoporotic process (Graph I). This graph shows that they were able to halt the disease process by estrogen therapy. It is also important to note that the loss of stature was steadily progressive when not treated, and that even when treated, the process was not reversed, just arrested.

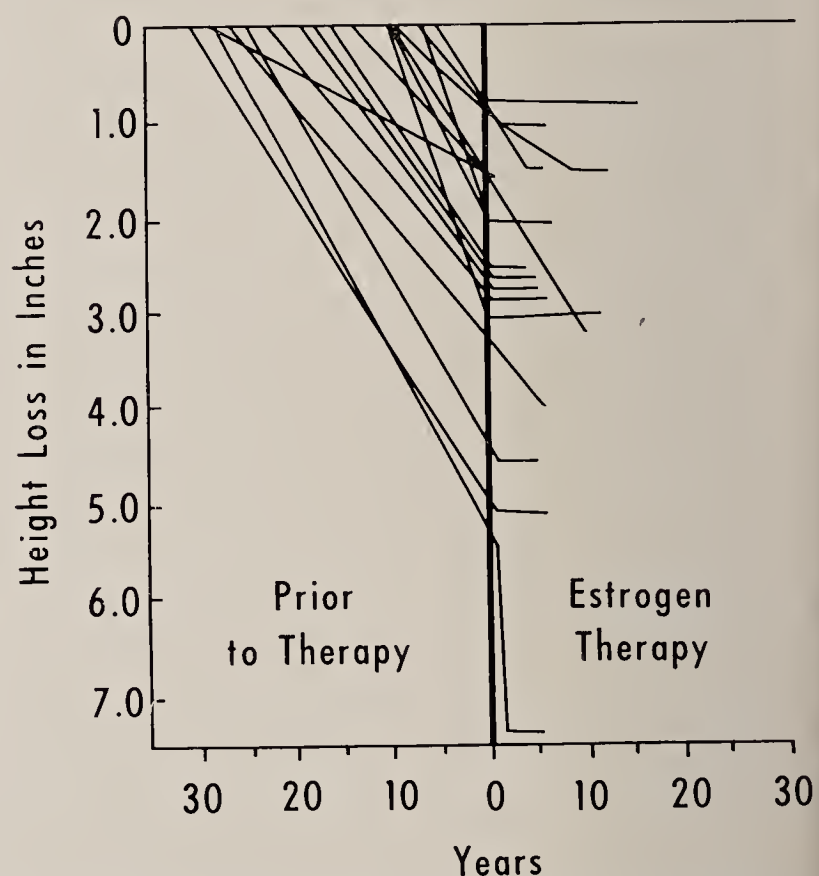


FIG. 1: Loss of Stature in Postmenopausal Women adapted from Wallach, S. & Henneman, P. H.: Prolonged Estrogen Therapy in Postmenopausal Women. J.A.M.A., 171: 1637, 1959.

A somewhat different approach was used by Davis, in Chicago. An iodine source with a scintillator as a detector was employed to obtain a densitometric index on a phalanx with correction for soft tissue. The degree of osteoporosis is plotted as a fall in the bone absorption coefficient μ^8 in CM^{-1} on Graph II. Davis feels that estrogen therapy staves off the onset of the disease for five to ten years, and thereafter retards its progression.

Further studies are necessary to establish the true role of estrogen therapy in the treatment of osteoporosis.

POSTMENOPAUSAL ESTROGEN THERAPY

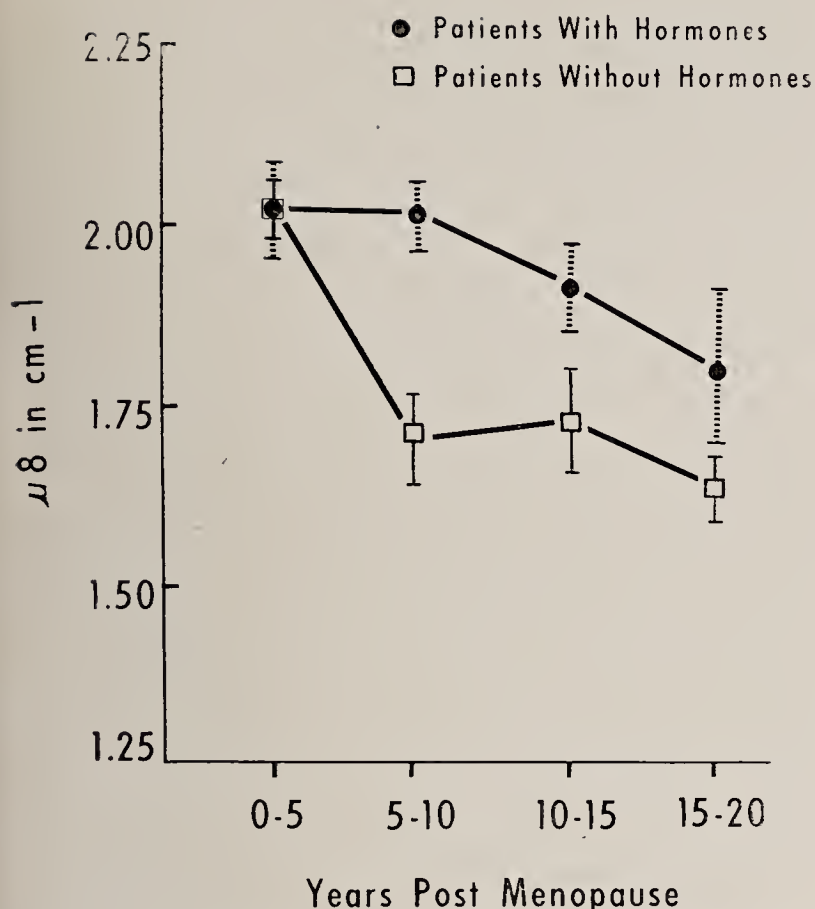


FIG. 2: Osteoporosis in Postmenopausal Women adapted from Davis, M. E.; Strandjord, N. M. & Lanzl, L. N.: Osteoporosis. J.A.M.A., 196, 1966.

Meema et al⁸ at the Toronto Western Hospital have developed a densitometric index which corrects for soft tissue and which measures cortex thickness and density separately. Early and as yet inconclusive work is being done with tracers on metabolically controlled patients. Perhaps a combination of these methods or even an entirely new one will eventually be used to answer the question objectively. Few clinicians today dispute the fact that estrogens are involved in the osteoporotic process, although their exact role remains to be clarified.

ATHEROSCLEROSIS

The relatively low incidence of atherosclerosis and its sequelae in pre-menopausal women has led to the postulate that estrogen prevents or retards this process. Experimental work using animals has tended to confirm this view. More recently, the role of the hormone in the atherosclerotic process in humans has come under study. Szaajdeman and Oliver⁸ reported a six to twenty year follow-up on thirty-five women who stopped menstruating spontaneously before the age of 40. The incidence of cardiovascular complications was seven times that found in a normal population, thus implicating lack of gonadal hormones in the disease process. Many experiments have been carried out using the ratio of serum cholesterol to phospholipids as an index of estrogen effect. Recently, doubt has arisen as to whether this ratio is at all meaningful, thus invalidating a number of studies.

Another approach has been used by Marmorston et al.¹³ They treated five hundred males who had a previous history of one or more myocardial infarctions with Premarin for twenty-four months. The group so treated had a 50 percent better long-term survival rate than that of the control group.

These results are impressive, but the feminizing effects of the drug, when administered in therapeutic doses, makes the treatment relatively useless for males—although it would seem to be warranted in females.

It has been shown by Dingman and Lin¹⁰ that hypercholesteremic subjects showed a significant increase in epiandrosterone excretion, but that other androgenic fractions were within the normal range. Estrogen therapy of hypercholesteremic postmenopausal females lowered the serum cholesterol to normal, and they suggest that this may be the result of a re-arrangement in enzymes which regulate the synthesis or degradation of cholesterol. Estrogens may affect the relative activity of these enzyme systems in both sexes. Since hypercholesterolemia has been associated with the early development of atherosclerosis, this thesis may explain the action of estrogen in preventing or retarding the atherosclerotic process.

Both clinically and experimentally, estrogen therapy appears to affect the onset and severity of atherosclerosis. At the moment, however, no one knows the optimal dose, time of commencement or duration of estrogen therapy. Until these questions are settled, the use of estrogen as specific treatment for this disease is probably only an investigational tool. On the other hand, the possibility of its anti-atherosclerotic effect is a bonus when long-term replacement therapy is instituted for other reasons.

CLIMACTERIC SYNDROME

The average woman is not concerned with her cholesterol /phospholipid ratio or the densitometric index of her radius. She is, however, vitally interested in the menopause and the loss of her figure. Popular magazines have capitalized on this interest by flooding the reading public with articles promising prolonged youth as well as freedom from the reputed horrors of the menopause. The general practitioner must understand both the problems of the menopause and the effect of estrogens on them before he can adequately answer a woman demanding therapy.

The climacteric syndrome (a more exact term than menopause) includes the symptoms experienced by women as their ovaries are failing. A typical classification is that of Greenblatt¹¹ (Table II). The cause of these symptoms is unknown, and their severity varies greatly. Some women barely notice "the change of life", while others never recover from it. This variance has probably both a physiological and psychological basis. Physiologically, there is probably a wide range of

susceptibility and sensitivity to vascular upset and metabolic disorders. Psychologically, this time of life is often very difficult for women. Their children have become independent, thus depriving them of their principal responsibility, and, in many instances, husbands are reaching the peak of their careers with less time for family life. Add to these factors the fear of old age which the menopause often signifies, and the result may be a severe emotional disturbance. Thus it has long been recognized that the treatment of the climacteric syndrome must be more than physiologic replacement of hormones.

TABLE TWO

Classification of Common Symptoms of the Climacteric Syndrome:

Disorders of the Autonomic Nervous System
(a) hot flushes
(b) sexual excess
(c) sweats
(d) spasms and globus hystericus
Psychogenic Disturbances
(a) apprehension
(b) insomnia
(c) nervousness
(d) headache
(e) frigidity
Metabolic Disorders
(a) bone demineralization
(b) myalgia
(c) skin and mucous membrane atrophy

The traditional treatment of this syndrome has quite logically varied with the severity of the symptoms. Mild sedation has been used for all but the most severe cases, where most clinicians agree that estrogen therapy may be indicated. It is also indicated in the treatment of atrophic vaginitis and atrophic rhinitis.

Although it has been known for many years that most of the climacteric syndrome could be avoided by the administration of estrogens, most clinicians did not like to use these hormones for this purpose. Two of the objections have been discussed above—"interfering with nature", and "carcinogenic effect". The most telling argument was that most women go through the menopause smoothly, without the need of therapy, hence why treat people who need no treatment? If, however, the long-term use of estrogens were to be introduced to prevent osteoporosis or even atherosclerosis, one of the "fringe benefits" would be the elimination of the subjective symptoms of the menopause.

FOUNTAIN OF YOUTH?

It is probably true the estrogen therapy will retard the aging process in the female genito-urinary system and the breasts. These drugs have been used to treat atrophic vaginitis and urinary incontinence due to the aging of the bladder trigonal area. "Dowager's hump" and other skeletal stigmata of old age are usually the result of the osteoporotic process, and hence can be delayed by a decade or more. The loss of feminine

contours — the result of shifting fat distribution — is probably due only in part to ovarian failure. The appearance of a woman in her fifties depends far more on her role in life during the previous forty years than on any drugs she is now taking. Thus, although estrogens can retard some aspects of the aging process, the total effect is dependent upon many other factors.

TREATMENT

There are three basic classes of estrogenic compounds available—biological, non-steroid and synthetic. Biological agents contain conjugated estrogens and are obtained by extraction from the urine of pregnant mares. These compounds are relatively inexpensive, but are not as pure or as effective as newer agents. Non-steroidal substances such as diethylstilbestrol are not true estrogens but rather compounds whose steric configuration is similar to that of the natural hormone, and hence, they have an estrogenic effect. Although inexpensive, these agents frequently cause nausea and vomiting. The synthetic estrogens have been made possible by the ability of chemists to synthesize compounds which are almost identical to the natural hormone. Although initially expensive, increased production and improved manufacturing techniques have lowered their cost. These agents are much better tolerated than earlier ones, and hence now appear to be the drugs of choice.

The pattern of therapy with estrogens is still a subject of controversy. Originally, they were given continually with no period of withdrawal. Unopposed estrogenic stimulation of the endometrium caused hyperplastic changes and led to breakthrough bleeding, usually within two months. The bleeding could be controlled with higher doses but eventually would recur. Sequential therapy is probably the most desirable form of estrogen supplementation, and could become feasible with increased demand by the public, and the cooperation of the pharmaceutical companies in the production of drugs.

Today, a number of different routines are in use, but all involve cycling in order to allow a period of withdrawal bleeding. Some authorities give estrogen for a specific period and then withdraw it, thus initiating flow. The length of the cycle may be an arbitrary one, or in some cases be determined by allowing bleeding to occur spontaneously on the first cycle. Estrogens when used alone, however, tend to cause heavy bleeding. By adding an anti-estrogen just before the end of the cycle the flow can be greatly reduced. Androgens have been used in this role, but their masculinizing effects are undesirable. Progestational agents are anti-estrogenic and do not have as many undesirable side-effects as androgens. Recently, an attempt has been made to duplicate the natural menstrual cycle using sequential therapy. Increasing amounts of estrogen are given throughout the cycle, with a progestational agent added

near the end. When bleeding is to occur, progesterone is withdrawn and a very low dose of estrogen continued. Thus, the normal ebb and flow of hormones level is duplicated. This method is complex, involving a variety of doses, and would be quite expensive.

The major problem, however, is not the agent or the pattern of treatment, but the dosage which is to be given. Low doses will give subjective relief from most of the symptoms of the climacteric syndrome. Higher doses, however, are thought to be required to control osteoporosis or atherosclerosis. Tolerance to these higher doses is extremely variable. Some women have no side-effects on a standard dosage schedule, while others have severe symptoms. The maturation index which can be used to measure the effect of estrogen and progesterone on vaginal mucosa is useful as a guide to dose levels. At present, in order to establish the proper regimen for a particular patient, the physician must carefully adjust the dosage schedule until both he and the patient are satisfied. This adjustment usually takes at least two months and often longer. In surgically castrated women, high doses of estrogen are easily tolerated if given within two years of the operation.

Another problem arises when the patient, who is being treated with replacement therapy, presents with mid-cycle vaginal bleeding. The usual treatment in this high-risk age group is a diagnostic curettage. However, if the problem recurs with further replacement therapy, how will these patients be handled? Certainly curettage can't be done on every patient biannually, but the possibility of malignancy can't be ignored. Many a practitioner who is treating a large number of postmenopausal women may find himself with little time for the rest of his practice. Thus, many problems will have to be resolved before replacement therapy can be made available to women generally.

CONCLUSION

Long-term replacement therapy for post-menopausal women is inevitable. Further research and demands of women will make this form of therapy quite common within ten years. Within this same period, I would expect the therapeutic value and treatment regimen for these agents, in diseases such as osteoporosis and atherosclerosis, to be more clearly delineated. However, at present, long-term physiological replacement therapy appears to be impractical for all but a few closely supervised patients.

SUMMARY

Estrogen therapy is no longer contraindicated because of the fear of its supposed carcinogenic effect. The philosophic question of whether the medical profession should tamper with nature seems irrelevant if the benefit of the treatment is established. Estrogen therapy appears to prevent or retard both osteoporosis and atherosclerosis; however, these effects are still not verified, and continue to be the subject of medical controversy. Easing of the climacteric syndrome and the prevention of both atrophic vaginitis and atrophic rhinitis are widely accepted indications for estrogen therapy. The agents, pattern of and dosage adjustment continue to pose problems which must be solved before replacement therapy on a long-term basis will be practical.

ACKNOWLEDGEMENT

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Clinical Applications Of Hormones In Pregnancy

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I DIAGNOSTIC APPLICATION

1) PREGNANCY TESTS

Most biological tests depend on the large amounts of chorionic gonadotrophin (CGT) in blood and urine during early pregnancy. They thus become positive about 2 weeks plus after the first missed menstrual period. As most are performed on urine, the often forgotten criteria of sample collection are reviewed:

1. Fluid intake should be restricted from eight o'clock at night until the specimen is collected the following morning.

2. The patient should void at bedtime, discard this specimen, and collect the first morning urine in a clean glass container.

3. The patient should not take any medication such as barbiturates, analgesics, or hypnotics, for forty-eight hours prior to the collection of urine.

4. At least 60 ml. of urine is required.

5. The urine should be kept in the refrigerator when not in use.

6. Any sample which is grossly bloody or contains a high protein concentration should be discarded.

A ANIMAL TESTS

i) *Aschheim-Zondek Test*

This test is time honoured, of high accuracy, but requires at least 3 days, and in doubtful cases histological sections of the ovary are useful, causing further delay.

ii) *Friedman Test*

The simplicity and speed of this test utilizing a non-pregnant female rabbit have made it exceedingly popular. Ruptured hemorrhagic follicles are a positive sign.

iii) *Ovarian Hyperemia Test*

The test using 2 immature female rats is rapid and simple, but accuracy depends on meticulous observation of precautions. The colour difference between ovary and fallopian tube 4-24 hrs. after intraperitoneal injection of urine is the basis of the test.

iv) *Male Frog Test*

CGT causes ejaculation of sperm into the cloaca of an adult male frog. However the amounts required are

relatively large, and thus the sensitivity of the test is low.

B IMMUNOLOGICAL TEST (BREVINDEX)

The Antiserum is a solution of anti-CGT antibodies. The antigen is a substance which reacts with anti-CGT antibodies coating latex particles. If the urine contains CGT, the CGT will combine with the antibodies and sequester them. Thus, when the antigen is added, nothing reacts with it, and the latex particles remain individual. Conversely, if there was no CGT to neutralize the antibodies, then an antibody—antigen complex will form, causing agglutination of the latex particles. This test is rapid, simple, inexpensive. Other than refrigeration of the test kit, no apparatus is required. The test is sensitive, becoming positive at 14 days and remains positive through the pregnancy.

C HORMONE WITHDRAWAL TEST

Technique—The female patient is given a combination estrogen progesterone tablet. The ingestion of gestational and estrogenic hormones promotes and increased blood supply to the surface endometrium, and withdrawal results in accentuation of the changes that lead to bleeding, if the patient is not pregnant. Consequently, if bleeding was induced, the test records a non-pregnant state. Failure to bleed indicates that a non-proliferative endometrium or decidua is present, and the test is positive for pregnancy.

D CHROMAGEN TEST

The newest of the laboratory pregnancy tests is based on a long known fact that pregnant urine plus iodide yields a rose coloured chromagen. Further modification showed that the chromagen could be stabilized in N-butanol. Thus was born "Pregna-Test Set". The active ingredient in urine is believed an estrogen—glucuronide.

The set is simple, can be quantitated, and is reported to exceed biological test accuracy in early pregnancy. False-negatives are supposedly eliminated, but false-positives do arise with people who have gynecological problems associated with increased estrogen production.

2) HYDATIDIFORM MOLE

Hydatidiform mole (proliferation of the epithelial covering of chorionic villi, with cystic degeneration of

an avascular stroma) is attended by a high concentration of CGT in blood and urine. These high concentrations merely reflect the proliferation of the Langhan cells. The normal CGT urine concentration has a broad peak when graphed, extending over days 45 - 85, and then a decline to relatively low levels. Thus the detection of mole CGT levels which are 10 - 100 times greater than the usually plateau levels must await 100 days after the LNMP.

This method of mole detection is basically sound. However, some moles will not produce excessive CGT and some may hypofunction. Thus false-negatives occur. Secondly, false positives occur, rarely in a normal pregnancy, but more commonly in the multiple pregnancy. Thus CGT levels is a test which may add to clinical suspicions but which is not per se an absolute index.

3) ESTRIOLS

Estriol is a member of the estrogen complex whose presence necessitates an intact fetal-placental relationship. Experimentation reveals that normal secretion levels determined from urine, exceed 12 mg./24 hours. Values less than 10 mg./24 hours indicate impending fetal jeopardy, while values below 4 mg./24 hours are compatible with fetal death. These values are less significant the earlier the gestation, but are absolutely true in the last 4 weeks, and relatively true in the last 8 - 10 weeks of pregnancy. As a corollary then, the fetus does play a part in estriol levels. The trend which repeat estriol determinations follow is significant. Any procedure done on the basis of a single laboratory value is inconclusive, since there is individual variation plus a 25% range of error for any value plus laboratory errors which give spurious values. (Fig. 1)

i) *Hydatidiform Moles*

The mole is not a fetus, and thus there is no fetal-placental relationship. Estriol levels are therefore consistently low or non-existent; eg.: 1 - 2 mg./24 hours on repeated samples.

ii) *Diabetes*

The diabetic mother is more susceptible to intrauterine death (i.u.d.) during the last 4 - 8 weeks of pregnancy. Postulated causes include placental decline of hormone production; poor control of the maternal disease, since control becomes more brittle as term approaches; and uterine ischemia. The cause is really not understood.

Nevertheless, daily estriol levels can give an index for impending i.u.d. and thus are used to decide on a time for induction or Caesarian Section. The value lies in using a more absolute index than just clinical impression to weigh the risk of prematurity against that of "expectant waiting".

iii) *Toxemia*

As in diabetes, the perinatal mortality rate is higher than in the non-complicated pregnancy.

Estriols give an index to follow, but the changes are not clear cut, and research is continuing to try and understand why this disease should distort the estriol level in its role as monitor of fetal jeopardy.

iv) *Post-Maturity*

The possible relationship between the post mature fetus and placental dysfunction has long been a subject of controversy where North America has been relatively unconcerned and Europe over anxious. Nevertheless there is no doubt that post maturity is associated with increased perinatal mortality. It is this which has caused American Doctors to examine ways of assessing the post-mature fetus.

Estriol levels are a good index to follow the post-mature patient, and thus to indicate either induction or section should jeopardy intervene.

v) *Repeated Unexplained I.U.D.*

There certainly exists the condition of habitual abortion, the term usually defined as the loss of 3 or more consecutive pregnancies.

Though we have no adequate treatment, we can follow the fetus with estriol levels, and deliver him before his intrauterine demise to face the risks of prematurity.

vi) *Erythroblastosis*

This is a disease of cross sensitization of the Rh negative mother by an Rh positive fetus, with resultant maternal production of antibodies which cross the placental barrier to destroy fetal red blood cells.

Estriols are a poor index of fetal jeopardy in this disease. The levels remain high until irreversible damage and fetal death occur, when they suddenly fall towards zero.

II THERAPEUTIC APPLICATIONS

1) ESTROGEN-PROGESTERONE THERAPY

i) *Infertility*

It has been empirically found and practically used by many doctors, that a 3 month course on "Birth Control Pills" leads to a hypersusceptibility for becoming pregnant. There is no sound physiological basis to cycle regulation and infertility resolution, but one cannot deny the results.

ii) *Threatened Abortion, Diabetes*

The theory of placental insufficiency (progesterone secretion decline) forms the basis for giving progesterone or estrogen-progesterone compounds in these cases.

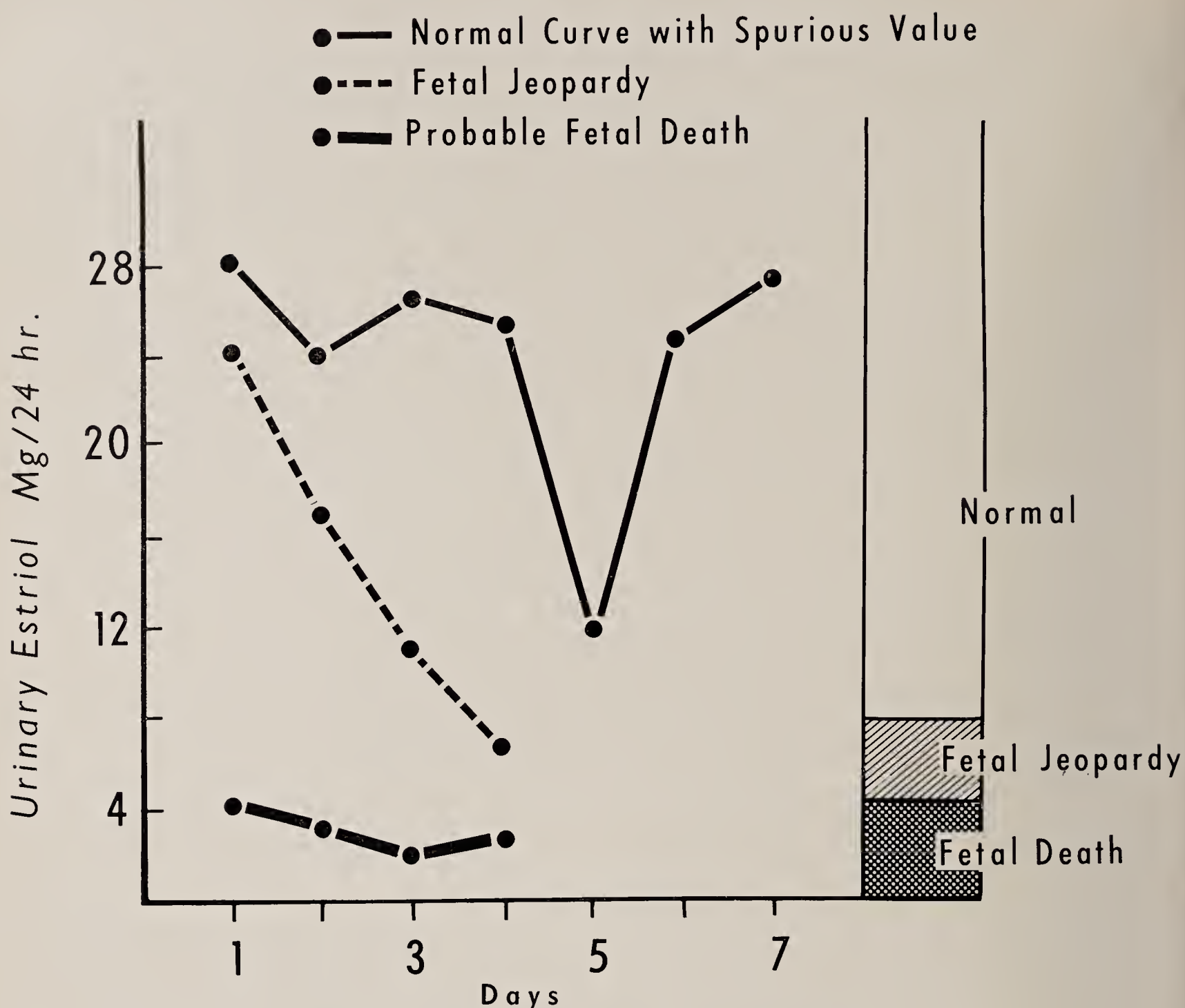


FIG. 1.: Urinary estriol determinations during pregnancy.

The use of the hormones is not a resolved issue. The literature parallels individual opinions—some believe that hormones give a lesser incidence of i.u.d. while others deny this.

It is interesting that although theoretical considerations and experimentation incriminate progesterone lack, many obstetricians state that estrogen administration alone gives results as good as progesterone or combined therapy.

The studies of Turner et. al. on hormone administration showed a definite rise in the levels of urinary metabolites of estrogen and progesterone when hormones were given during pregnancy. However, when such patients are followed into the post partum period, their hormone levels are lower than controls and remain so longer, their endometrial response to circulating hormone levels is poor, and they have a greater incidence of dysmenorrhea and menstrual irregularity. Thus the hormone coin is a two sided one.

Though experimenters can measure maternal blood and urine hormone levels and show that these rise, this is no proof of an increased maternal-fetal response. Estrogen, as noted in the physiology of estrogens, is largely secreted by the placenta to the fetus. One then wonders how much benefit hormones given to the mother achieve, since they must face the placental barrier and most never reach the fetus.

The solution to this controversy has not been found, but this is an avenue of investigation whose course will be interesting to follow.

2) OXYTOCIN AND LABOR

i) Induction of Labor

In the past, oxytocin was a crude extract given by the intramuscular, nasal or subcutaneous routes. With the introduction of the dilute intravenous standardised solutions (eg.: Syntocinon, Pitocin), there has been an

evolution. Presently, some obstetrical centres deliver more women by scheduled oxytocic inductions than by spontaneous onset of labor.

Studies reveal that provided the cervix is favorable, that the vertex is dipping into the pelvis, and that there is no cephalopelvic disproportion, elective induction carries no greater and possibly less risk than spontaneous labor.

The uterus is relatively insensitive to oxytocin before 20 weeks. Thereafter, sensitivity rises until 36 weeks when it plateaus. Thus, to achieve equal uterine work, more oxytocin is required the more immature the pregnancy. Furthermore, since progression of labor requires a ripe cervix which in turn necessitates uterine work, the less favorable the cervix, the more drug needed to flog the uterus.

The optimal clinical features to look for include moderate to severe contractions recurring every two to three minutes and lasting forty-five to sixty seconds. The uterus should relax completely between contractions.

Usually the dose should not exceed 16 milliunits per minute. However, occasions where larger doses are indicated are induced abortion (pregnancy or mole) and hemorrhage post partum or post abortion. Once active labor commences, the drip is stopped.

ii) *Third Stage of Labor*

Oxytocic drugs (eg.: Syntocinon 10 units) are routinely given after delivery of the fetus to expedite placental delivery, to minimize uterine bleeding, and as prophylaxis against post partum hemorrhage.

iii) *Post Partum Hemorrhage*

In any case of PPH, the cause as well as the signs must be treated. The commonest causes of early bleeds are:

1. Uterine atony
2. Retained membranes or placental tissue
3. Unrecognised lacerations
4. Bleeding from the placental site.

Of the listed causes, oxytocin is of curative value in uterine atony and to a lesser extent in placental site bleeding. (For placental site bleeds, ergot compounds which have an effect on the lower uterine segment which is usually the site of bleeding are more useful). In all cases of PPH, oxytocics are justified to produce uterine contraction as a means of controlling the bleed.

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Abstract

Vascular Hypertonicity

A Mechanism for Vasodilatation in the Dumping Syndrome. C. E. Lucas, R. C. Read. *Surgery* 60: 395-401. Aug. '66.

It has been observed that the symptomatology of the dumping syndrome is accompanied by peripheral vasodilatation; the mechanism of this peripheral vasodilatation seen in the dumping syndrome was studied in dog and man. Experimental dumping was produced by the intraduodenal administration of 150-200 ml. of 50% glucose or 10% sodium chloride using isotonic fluids or intragastric injection as controls. The question whether a vasodilatory substance was released into the bloodstream was investigated with the use of the in situ isolated perfused kidney. Hyperosmolality was achieved in this group of experimental animals by means of both intraduodenal and intravenous administration of hypertonic fluids. Human volunteers both with and without an ulcer diathesis were similarly studied post-operatively, after normal gastrointestinal function had returned.

The results demonstrate a significant increase in vascular osmolality during dumping in both man and animals which is associated with a fall in both systemic pressure and isolated renal vascular resistance. These latter changes were of the same magnitude whether corresponding degrees of hyperosmolality were achieved by glucose or salt administration and by either intraduodenal or intravenous injection. These findings support the concept that vascular hyperosmolality in itself provides a significant vasodilatory stimulus in the dumping syndrome.

The hypothesis for vasodilation involves a direct action on peripheral vascular smooth muscle or even capillary walls as a result of cellular dehydration. A further hypothesis was suggested: that there is an important osmoreceptor center located in the pylorus which prevents the rapid release of hypertonic gastric contents into the small bowel until considerable intragastric dilution has occurred, and that the dumping syndrome occurs which this mechanism is disrupted.

R.I.H.

Estrogen Biosynthesis And Metabolism In The Feto-Placental Unit

I INTRODUCTION

During human pregnancy increasing amounts of estrogen—virtually all of which is elaborated by the syncytial cells of the placenta—is excreted in the maternal urine. There must be adequate fetal circulation to sustain this estrogen synthesis by the placenta. In view of recent clinical applications of serial urinary estriol assays in assessing feto-placental viability,¹ this article will concern itself with describing some of the metabolic interrelationships between the mother, placenta and fetus with specific regard to estrogens. The material herein is derived largely from numerous reviews on this subject by Egon Diczfalusy,^{2 3 4 5} in whose laboratory in Sweden most of this work was done.

For the past two summers the author has been utilizing the ammonium sulphate precipitation technique of urinary estrogen assay⁶ in order to study some of the estrogen sulfate conjugates in late pregnancy urine. During this time there was the opportunity of becoming acquainted with the experimental design of pre-viable fetal perfusion with labeled steroids, and their subsequent chemical analysis.

II GENERAL PATHWAY OF STEROID BIOSYNTHESIS

The scheme shown in Fig. 1 will serve as a basis for the discussion to follow by illustrating some of the key

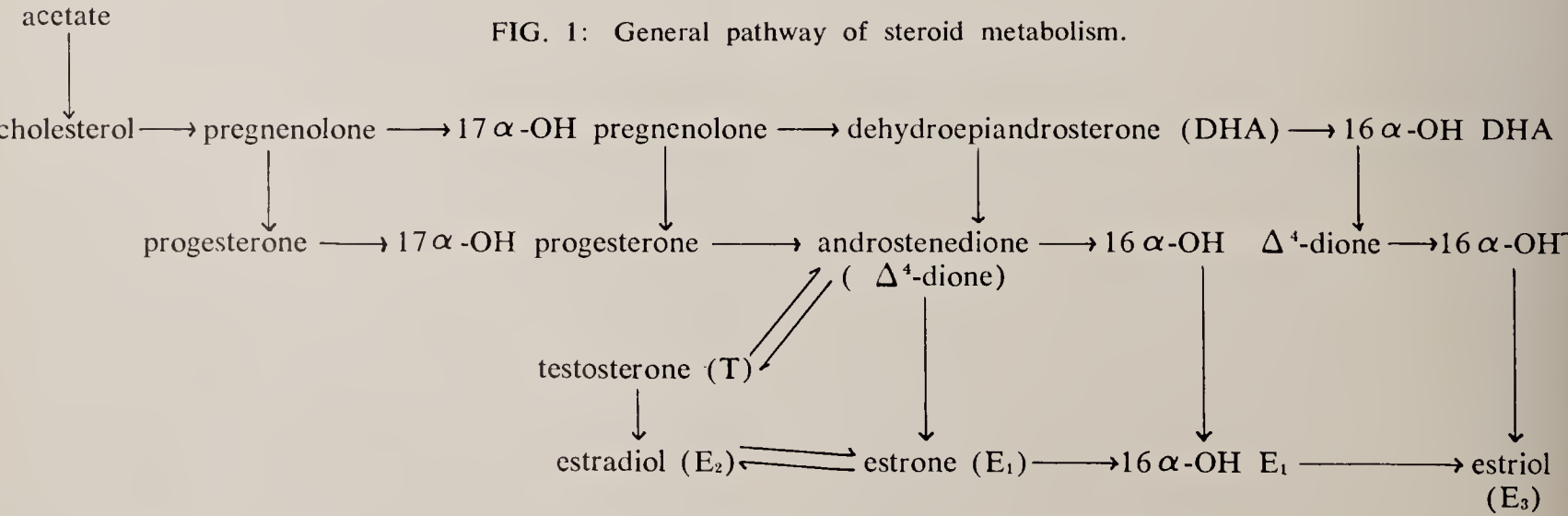
reactions involved in the biosynthesis of estrogens. It must be recalled that acetate and cholesterol can be precursors of all steroid hormones.

III ESTROGEN BIOSYNTHESIS AND METABOLISM IN THE FETO-PLACENTAL UNIT

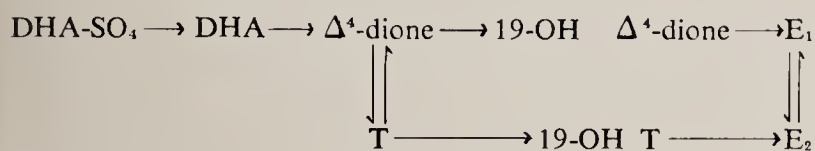
Estrogen biosynthesis from acetate by perfused term or mid-term placenta in situ has not been demonstrated.⁷ Similarly, conversion of progesterone to estrogen by the intact feto-placental unit in situ has been shown not to occur.⁴

The placenta, however, does contain an enzyme system capable of converting neutral (i.e. non-phenolic) C19 steroids to estrogens by aromatization of ring A of the steroid molecule. It has therefore been postulated that the principal route of estrogen biosynthesis by the placenta may consist of aromatization of neutral steroid precursors reaching the placenta by the fetal and/or maternal circulations. Thus, by perfusion of the intact placenta after removal of the fetus by therapeutic abortion, Bolté et al.⁸ have shown a significant conversion of dehydroepiandrosterone (DHA), androstenedione (Δ^4 -dione), and testosterone (T) to phenolic estrogens, but with the important observation that there was no conversion to estriol (E_3) or 16-OH estrone (16-OH E_1). It is apparent then that the placenta lacks the

FIG. 1: General pathway of steroid metabolism.



enzymes necessary for 16-hydroxylation. Therefore the following pathway has been suggested for the biosynthesis of estrone (E_1) and estradiol-17 beta (E_2) in the human placenta:



The result of this mechanism seems to be conversion of most androgens in the fetal circulation to estrogens.

Bolté et al.⁹ have similarly shown by perfusion of the intact feto-placental unit via the uterine artery prior to therapeutic abortion, that most maternal neutral steroid precursors are converted to phenolic material (mainly E_1 and E_2); but in contradistinction to perfusion of the placenta alone, small amounts of 16-hydroxylated phenolic compounds (mainly E_3) were also isolated. The conclusion is that neither the fetus nor the placenta alone, but rather the feto-placental unit is responsible for the formation of E_3 . Maternal androgens, therefore, reach the fetus as phenolic material and E_3 is formed by 16-hydroxylation activity in the fetal adrenal cortex and to a smaller extent in the fetal liver. However, Bolté et al.¹⁰ demonstrated that the conversion of neutral steroids from the feto-placental circulation is much greater in extent than that from the maternal compartment.

IV GENERAL CONCEPT OF ESTROGEN SYNTHESIS AND METABOLISM BY THE FETO-PLACENTAL UNIT

According to this scheme, Fig. 2, both maternal and fetal 3 beta OH- Δ^5 steroids such as DHA-SO₄ enter the placenta and are converted to DHA by sulfatases and in subsequent reactions to E_1 and E_2 via Δ^4 -dione (or 19OH-T) by 3 OH-steroid dehydrogenases and aromatizing enzymes. The E_1 and E_2 which are secreted into the mother are metabolized according to classical pathways and the portion transferred to the fetus is extensively sulfurylated and 16-hydroxylated mainly in the fetal adrenal cortex to diminish the estrogenic activity of these compounds. The E_2 is converted directly to E_3 and the 16OH- E_1 is transferred to the placenta where conversion to E_3 takes place by 17 OH-steroid dehydrogenases. The E_3 is then transferred to the maternal organism where it contributes to the E_3 pool of pregnancy and to the fetus where it becomes extensively sulfurylated.

The other pathway of estriol synthesis in the human feto-placental unit,—and this may in fact be the more important mechanism—is by the formation of 16OH-C19 intermediates of DHA and its metabolites, which are subsequently aromatized by the placental enzyme systems to phenolic steroids—mainly E_3 .

This concept explains:

- (1) the very high concentration of estriol in pregnancy urine paralleling the size of the fetus and/or the fetal adrenal cortex,
- (2) the marked drop in urinary estrogens after pregnancy,
- (3) the marked drop in estriol excretion in females pregnant with anencephalic monsters with atrophic adrenal cortices,^{11*}
- (4) the lower than normal, but still greater than in the non-pregnant condition, maternal E_3 excretion in hydatidiform mole, since the contribution of the fetal compartment in this condition would be absent,¹¹
- (5) the low E_3 levels following fetal distress or death due to the great sensitivity of the enzyme systems responsible for the production of phenolic steroids to changes in oxygenation and nutrition,
- (6) the relatively normal E_3 excretion in pregnant women with Addison's disease.¹² Thus the maternal adrenal contribution to estrogen precursors cannot be the significant one.

V FUNCTIONS OF ESTROGENS IN PREGNANCY

Despite what is known about these complex interrelationships of steroid metabolism among mother, placenta and fetus, the physiological significance is still a mystery. Several functions of estrogens in pregnancy have been postulated:

- (1) promote rapid uterine growth.
- (2) estriol may counteract excessive uterine stimulation by estrone and estradiol-17 beta.¹³
- (3) estriol prepares the lower reproductive tract for delivery.¹⁴
- (4) regulation of certain phases of placental and endometrial metabolism.¹⁵

VI SUMMARY

The activity of the placenta in estrogen metabolism is largely confined to conversion of maternal and fetal neutral steroid precursors such as DHA-SO₄ to estrogens by aromatization of ring A of the steroid molecule. It is believed that the contribution of the fetal circulation

* It is important to recall that in humans there is a relatively large provisional juxtamedullary fetal adrenal cortex with a secretory pattern that is largely androgenic and which is normally replaced after the sixth month of gestation by the permanent adrenal cortex. The cause of this involution is unknown but may be related to decreased stimulation by human chorionic gonadotropin.

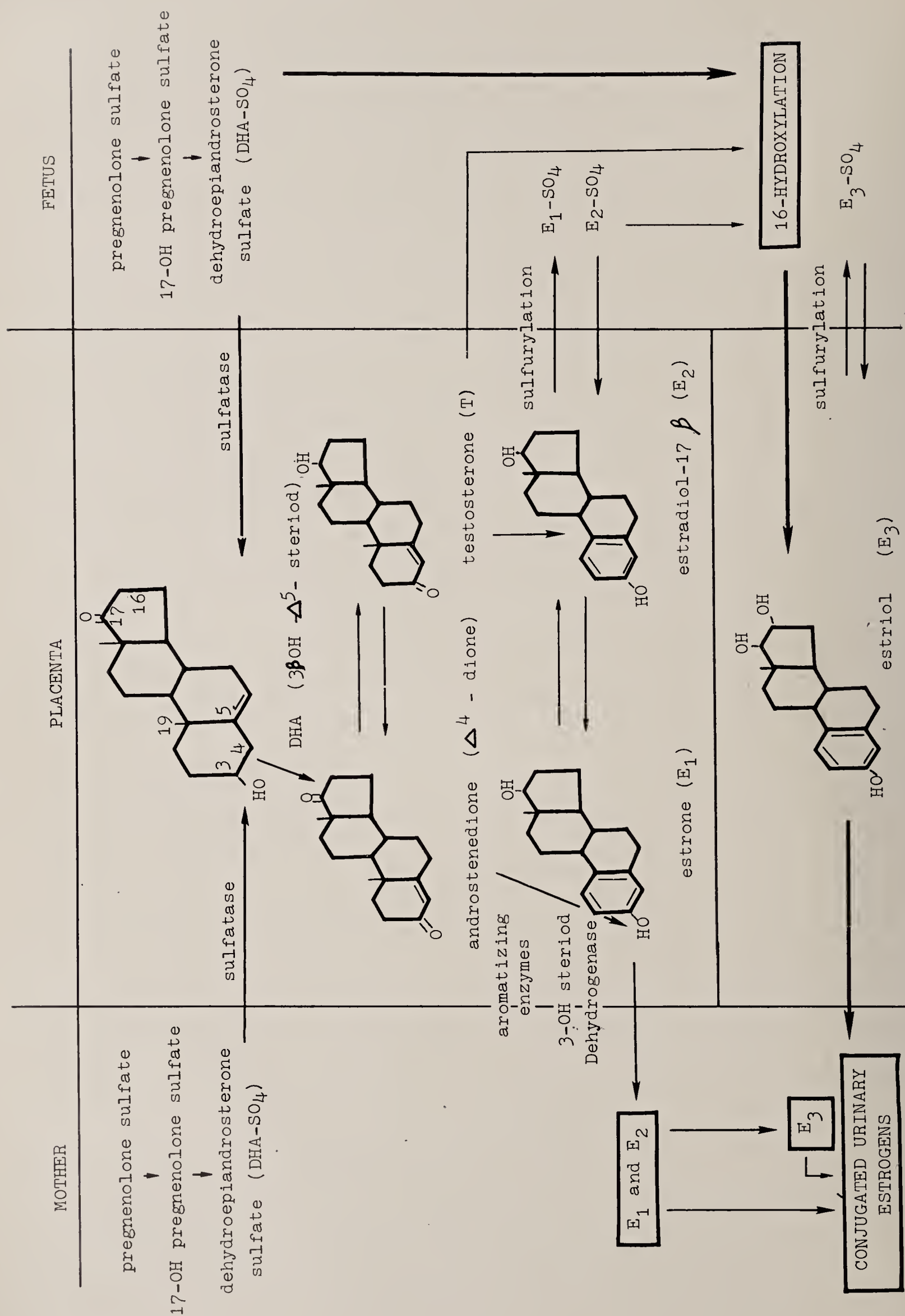


FIG. 2.: General concept of estrogen synthesis and metabolism by the fetoplacental unit.

STUDENT RESEARCH

is quantitatively the more significant. The formation of increasing amounts of E_3 during pregnancy is dependent on the 16-hydroxylation activity of the fetal adrenal cortex and if this is compromised in any way, decreased amounts of E_3 are excreted in the maternal urine. This is of some importance in clinically assessing fetal viability.

H. Vellend 6T8

ACKNOWLEDGEMENT

I am indebted to Dr. S. L. Cohen and to Dr. R. Wilson for giving me the opportunity of working in the Steroid Laboratory in the Department of Obstetrics and Gynecology and for their invaluable guidance and inspiration.

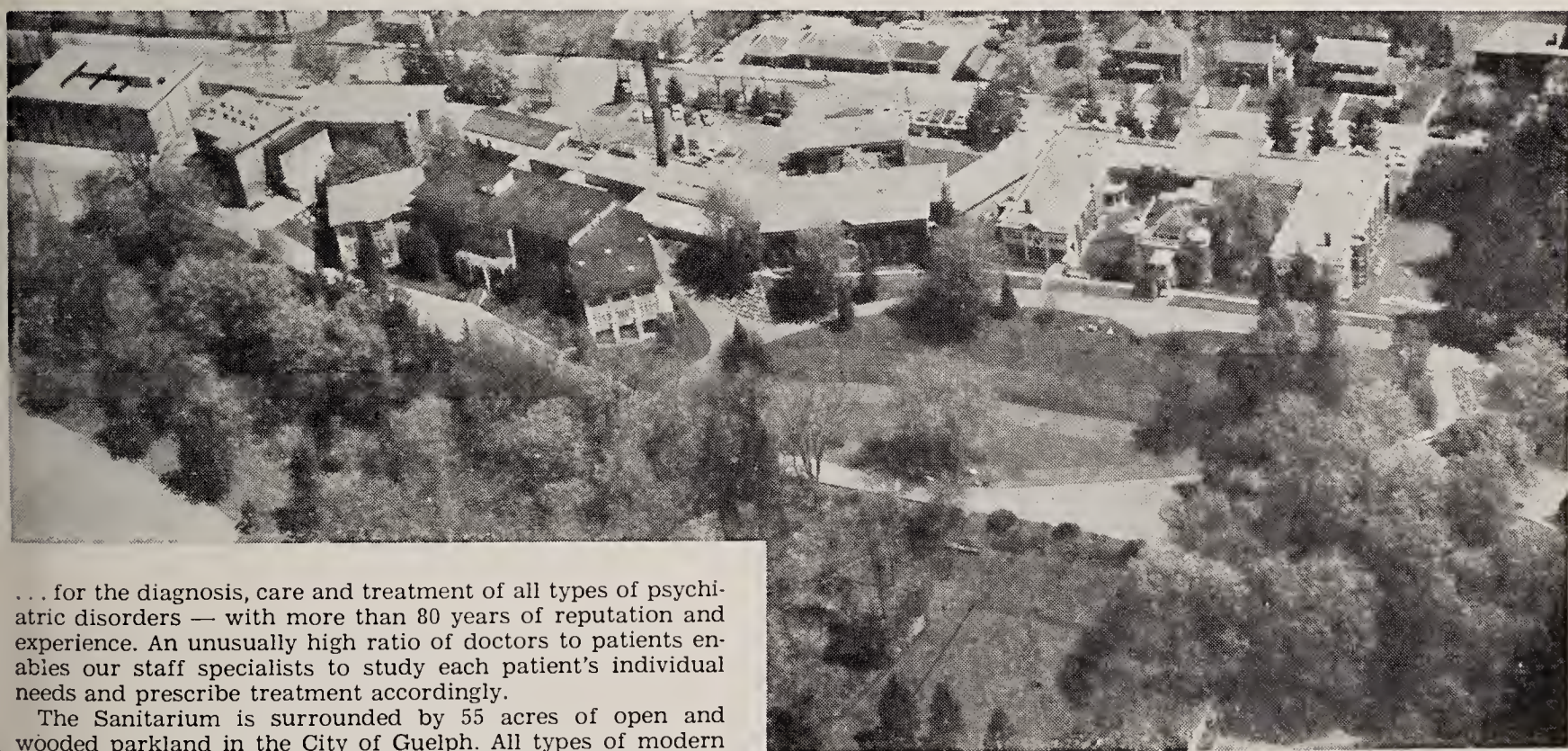
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Non-Clinical Methods Of Fetal Assessment

A. Dvorak 6T7

Several new methods have recently become available to aid the clinician in fetal assessment. However, the clinical methods (abdominal palpation, vaginal and rectal palpation, auscultation, inspection of amniotic fluid after rupturing membranes) still remain the mainstay; the new methods are an aid but not a substitution. This article presents a review of the more recent investigative techniques which may be used when clinical methods are inadequate.

1. LABORATORY METHODS

(i) PROCEDURES ON THE AMNIOTIC FLUID

It has been found that certain characteristics of the amniotic fluid are helpful in the diagnosis and management of hemolytic disease of the newborn. When a *spectrophotometric examination* of the amniotic fluid is done, absorption peaks are found in the vicinity of 415 and 450 m μ . The first peak results from oxyhemoglobin and the second from bilirubin. An increase in the height of this second peak, or its shift above this point, correlate well with the severity of fetal hemolytic disease, and may be an indication for the premature induction of labour or intrauterine fetal transfusion. *Cytologic examinations* of the amniotic fluid have been done of an experimental basis to estimate fetal maturity. It was found that the percentage of mature cells which stain orange with Nile Blue increases and that this increase is related to the functional maturity of the sebaceous glands, which correlates with the maturity of the internal organs.

(ii) PROCEDURES ON THE MATERNAL BLOOD

Maternal isoimmunization with fetal antigens and subsequent passage of maternal antibodies to the fetus may cause hemolysis of fetal red cells. This isoimmunization can theoretically occur with any antigen present in the fetus and absent in the mother. In practice, with rare exceptions, such isoimmunization can occur only with A or B antigens in the mother of blood group O, and with the D fetal antigen in the Rh negative mother. Therefore the determination of Rh antibody titres during pregnancy is of value. Two procedures can be done: the *Rh antibody titre* and the *indirect Coombs test*. Antibodies to saline suspended Rh⁺ cells (complete antibodies) apparently do not cross the placenta. Antibodies to Rh⁺ cells suspended in albumin or a similar solution and those detected by the indirect Coombs test (incomplete or blocking antibodies) are responsible for hemolytic disease of the newborn.

Every obstetrical patient should have a determination of her blood type and Rh factor. If her blood type is O or Rh negative, the same tests should be carried out on her husband. If the mother is Rh negative and the husband Rh positive, the antibody titre should be determined as early as possible in pregnancy to see if sensitization exists. A second determination is advisable at about 34 weeks gestation. The time of appearance of the antibody, and its titre are of importance.

It may be possible to forecast the fetal hydrops by measuring the *serum chorionic gonadotropin*. Levels around 100,000 IU per litre are indicative of the severe form of this disease.

(iii) PROCEDURES ON THE MATERNAL URINE

In pregnancies complicated by diabetes, intrauterine fetal loss is still several times that of the normal obstetrical population. Frequent or daily measurements of the urinary estriol *excretions* will permit a marked reduction in such losses since in utero death invariably is preceded by a fall in estriol excretion. Interruption of pregnancy by Caesarian Section in the 34-36 week of pregnancy had been advocated for the diabetic with vascular disease. When normal amounts of estriol are excreted there is minimal risk to the fetus and the patient may be allowed to carry the pregnancy to a greater degree of maturity. Estriol excretion may also be useful in following women who suffer from hypertension, renal disease, toxemia of pregnancy or Rh isoimmunization.

(iv) FETAL BLOOD SAMPLING

It is possible to obtain a sample of capillary blood from the presenting part of the fetus, before and during labour, provided that the membranes are ruptured. Fetal blood sampling therefore enables the obstetrician to assess more exactly the significance of changes in the fetal heart rate and the appearance of meconium in the amniotic fluid. It is unusual for a *fetal pH* of more than 7.2 to be associated with a baby whose condition is depressed at birth. Thus acid-base values of blood obtained from the fetal scalp during labour provided a means of detecting fetal asphyxia. The difference between the maternal and the fetal *base deficit* provides an index of the severity of the asphyxial depression. It may be of value in assessing the significance of a fetal pH reading. A metabolic acidosis, in contrast to a respiratory acidosis (of maternal origin) is associated with a more depressed baby at birth. It has been found

that these methods may occasionally result in the salvage of a fetus in the absence of clinical signs of fetal distress.

2. X-RAY EXAMINATION

(i) *Aid to diagnosis of fetal death.* The three principal x-ray signs of fetal death are: a) overlapping of the bones of the fetal skull, b) exaggerated curvature of the fetal spine, c) demonstration of gas in the fetus.

(ii) *Aid to the diagnosis of multiple pregnancy.* When two fetuses are suspected an x-ray is taken almost routinely. Unless pregnancy is too early or hydramnios too marked the additional fetus or fetuses are almost always visualized.

(iii) *Aid to the diagnosis of presentation and position.* In obese women or those with rigid abdominal walls this method may solve diagnostic problems and lead to an early recognition of a breech or shoulder presentation.

(iv) *Investigation of hydramnios.* It may be impossible to palpate the fetus due to severe hydramnios. X-ray examination may discover fetal abnormalities or a multiple pregnancy. Only hydramnios will be associated with pregnancy, in differentiating it from ascites or cyst.

(v) *Aid to the diagnosis of hydrocephalus.* On the x-ray one will see that: a) the face of the fetus is small in relation to the large head, b) the cranium tends to be globular, where the normal head is ovoid, c) the shadow of the cranium is thin and scarcely visible.

(vi) *Aid to the diagnosis of abdominal pregnancy.* Where the pregnancy is extra-uterine, the fetus is usually displaced to an unusual attitude or position. The shadow of the uterine wall may be absent. A lateral view may show the fetal parts overlying the maternal vertebrae. A strong suspicion may be confirmed with instillation of radiopaque material in the uterus, a dangerous procedure in the presence of intrauterine pregnancy.

(vii) *X-ray pelvimetry.* This procedure is used as an adjunct to the management of a patient with suspected contracted pelvis.

(viii) *Placentography.* Various methods are available: a) soft x-ray technique, b) intravenous injection of radioisotopes (Na^{24} , I^{131})—localization depends on a high count over the intervillous space because of a pooling of blood in that area, c) arteriography—radio-paque material is injected by way of the femoral artery, and a series of exposures is taken; the spurts at the end of the spiral arteries will identify the placenta.

3. FETAL ELECTROCARDIOGRAPHY

There are two methods of recording the fetal electrocardiogram. The first uses leads which are attached to the maternal abdomen; the second involves an electrode

directly in contact with the fetus. In the method utilizing the maternal abdomen, the electrodes are usually applied in the midline. The upper electrode is placed over the fundus of the uterus and the lower just above the symphysis pubis. Some systems also require a third electrode which is applied to the mother's leg. The ECG obtained contains both a maternal and a fetal complex. Only rarely does the abdominal wall electrocardiogram contain fetal P and T waves. Often the fetal QRS complex is of low amplitude. In the second method there are several approaches of placing the electrode in contact with the fetus. The electrode is most commonly placed in contact with the fetal scalp or buttocks; this can be done through the vagina and cervix during labour. An electrode can also be introduced directly through the mother's abdominal wall and uterus and directly implanted in the fetal buttocks.

Some applications of fetal electrocardiography include:

(i) *Diagnosis of Fetal Life*

The accuracy of diagnosis of fetal life is a function of the stage of gestation and the number of determinations made. It is helpful in a limited number of patients of less than 16 weeks gestation, at a time when x-ray examination and auscultation of the heart sounds are of little value. This procedure has some limited use in problem cases which involve suspected fetal death in utero, especially if a previous ECG had been obtained from the fetus. Twins have been diagnosed as early as 16 weeks of gestation. Fetal heart rates often differ from each other to a sufficient degree so that they will be separately recorded on a fetal ECG tracing.

(ii) *Aid to the diagnosis of fetal distress.* The normal fetal heart rate is 120-160 beats per minute. A fetal heart rate below 100 beats per minute constitutes evidence of fetal bradycardia and distress. It should be noted however that a normal slowing of the fetal heart rate may occur at the time the uterus contracts in labour. Bradycardia is not considered evidence of fetal distress if it disappears within 30 seconds after the uterus relaxes. It is only fetal bradycardia that persists at a rate below 100 beats per minute in the interval between uterine contractions that is considered significant. However, a fetal heart rate below 120 beats per minute is an indication for observation. Fetal tachycardia (a rate above 160 beats per minute) as a sign of fetal distress has been a subject of controversy. Although a transient tachycardia may be insignificant, experimental evidence indicates that a transient tachycardia is sometimes the first sign of hypoxia, and may be followed by a bradycardia when the hypoxia becomes profound.

(iii) *Other possibilities.* It is hoped that fetal electrocardiograms may aid in the diagnosis of presentation and of congenital heart disease. As yet the methods are not as accurate as these procedures require.

4. ULTRASOUND

Fetal x-ray examination may be avoided in some instances when ultrasonic examination of the uterus is done. In other instances it may be used as an adjunct to x-ray examination. Ultrasound pulses are repeated 1000 times per minute and the echos are recorded between one pulse and the next. Structures 2.5 mm. apart can be clarified. The fetal skull and trunk can always be identified but it is not yet possible to record the placenta accurately.

Ultrasound may be indicated:

- (i) When a *multiple pregnancy* is suspected.
- (ii) As an aid to the diagnosis of *hydatidiform mole*. Some authors believe that a characteristic pattern results from the ultrasound examination of a hydratidiform mole.
- (iii) Detection of *fetal abnormalities*, such as fetal acrania.
- (iv) Aid to the diagnosis of *hydramnios*. In the presence of hydramnios the fetal limbs appear separated from the fetal body, and the fetus appears separated from the uterine wall.
- (v) Diagnosis of *uterine abnormalities* in pregnancy, such as a septate uterus.
- (vi) *Fetal cephalometry*. This is a safe, simple, and accurate method of measuring the biparietal diameter of the fetus in utero. This method is especially appli-

cable in a breech presentation where cephalometry by x-ray is not very accurate. A transducer is moved over the maternal abdomen until two strong and equal echos produced by the nearly parallel parietal bones are obtained. The distance between the two reflections is the biparietal diameter.

5. THERMOGRAPHY

Thermoplacentography is a recent method of placental localization. Its place in clinical medicine is not yet certain. The increased blood flow and active metabolic state result in an increase in temperature at the placental site. This causes an increase in the emission of infrared radiation from that site. The infrared radiation can be converted to light which is recorded on a polaroid film, or it can cause a change in the colour of a heat sensitive dye which is applied directly to the skin.

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Recent Advances

Radioisotopes And Fetal Assessment

One of the most common causes of third trimester bleeding is placenta previa or a normal placenta implanted in an abnormal location. At one time the only method available to confirm the diagnosis was intra-cervical digital examination, but this often precipitated sudden, massive, hemorrhage. With advances in the field of radiology new techniques became available to help diagnose and assess the problem. X-ray placentography is about 95% accurate after the thirty-fifth week of gestation but prior to this the results are much more open to question and it is in this period, i.e. the first half of the last trimester, when the condition requires most aid.¹ The most recent advance in this field has been the use of radioisotopes and although slow to gain acceptance in many centres because of potential danger to mother and fetus, this technique is rapidly gaining popularity because of its consistently good results.

PRINCIPLES AND METHODS OF
RADIOISOTOPE PLACENTOGRAPHY

The use of isotopes for placental localization is based on the concept that the placenta is a large pool of maternal blood. When the maternal circulation is

tagged with a radioactive isotope there will be a local accumulation in the placental pool and this can be detected by appropriate techniques to be discussed presently. In Browne's original papers describing the technique², he used Na²⁴ but there were severe limitations because of the very short half-life of the isotope and the rapid diffusability of the sodium into the intercellular space. In 1957, Wineberg et al used radioactive iodine (I¹³¹) bound to albumin, i.e. radioiodinated human serum albumin (RIHSA), with considerably better results.³ This is the main isotope used to-day although studies are being conducted with I¹²⁵, I¹³², technetium^{99m}, and chromium⁵¹.^{1 4 5}

The tracer isotope is injected into the antecubital vein and a period of up to 15 minutes is allowed for mixing with the maternal circulation. For purposes of diagnosis the abdomen is divided into several segments and radioactivity over each is determined. The count is usually expressed as a percentage of the count over the xyphoid process. The number of sectors into which the abdomen is divided varies from nine⁶ to twenty-one⁷. Typical results are recorded in Figures 1 and 2.

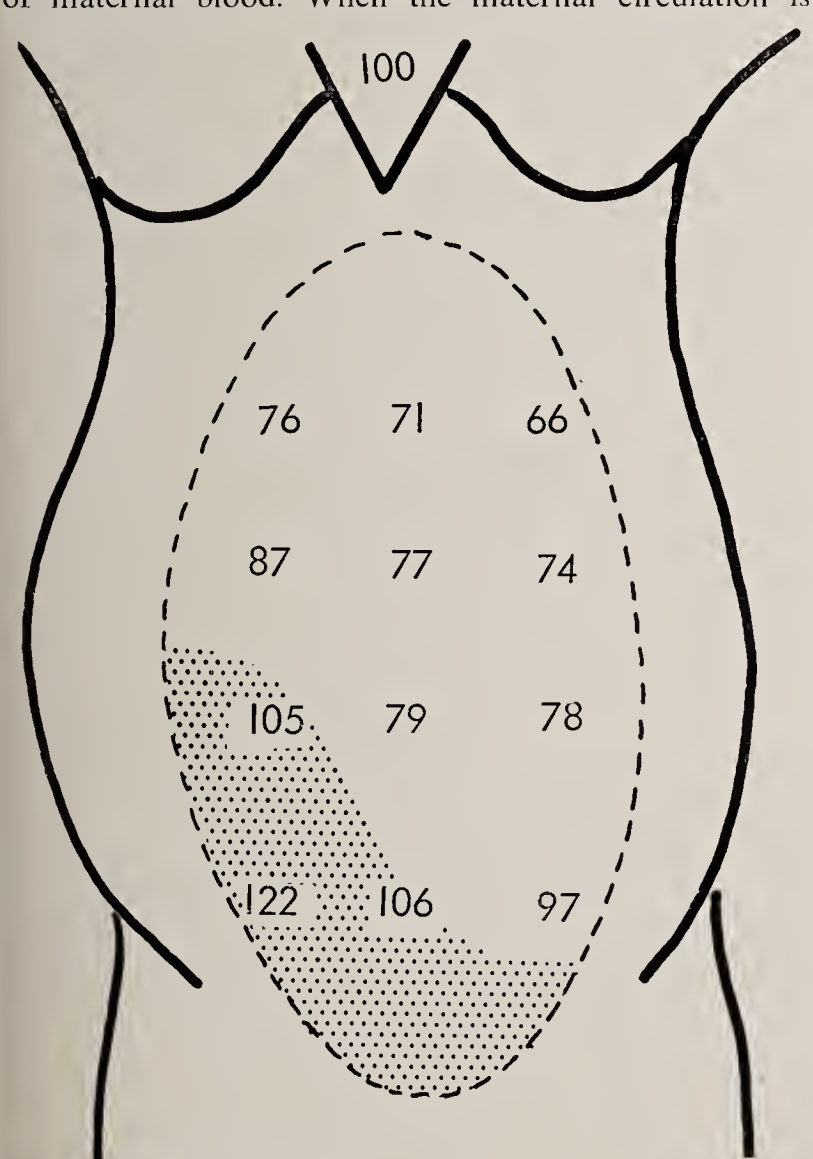


Fig. 1: Average reading . . . 94.
Diagnosis: Placenta localized on right lateral and anterior wall of lower segment of uterus. Total placenta previa.

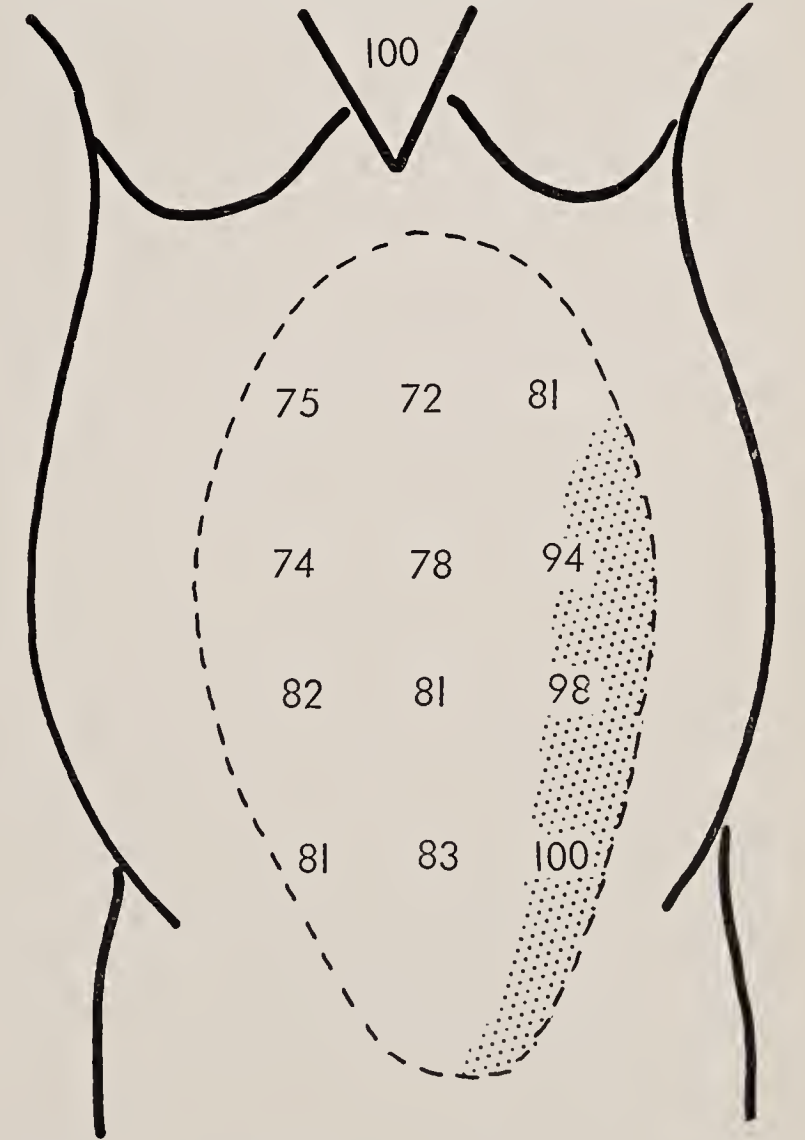


Fig. 2: Average reading . . . 86.
Diagnosis: Placenta localized on left lateral and anterior wall of lower segment. Partial placenta previa.

When the placenta is situated on the anterior wall of the uterus, its site is indicated by a region where the counting rate is considerably more than over the remainder of the uterus. If such a region is not found, it is concluded that the placenta is located on the posterior wall. Posterior locations can be clarified, however, by readings taken on either side of the uterus, i.e. at the maternal flanks. Usually the counting rate is decreased over the lower abdomen as compared to the fundus and if the opposite is obtained it is reasonable to suppose a placenta previa. In cases of intrauterine death there will be no localization because the placental circulation has shut down.³

ISOTOPE CONSIDERATIONS

The choice and dosage of isotope is critical because of the potential danger to both mother and fetus. Iodine-131 has a half-life of 8.08 days. When bound to albumin the iodinated complex mixes readily with the blood pool but is prevented from crossing the placental barrier because of the large size of the albumin molecule. Because of the half-life and the stability of the albumin molecule the concentration of radioactivity in the placental pool lasts for hours and this permits a longer counting period and reproducible scans.⁸ Some degradation of the albumin does occur however and this releases I^{131} which is then free to cross the placental barrier. It then becomes available for absorption by the fetal thyroid and if taken up can lead to serious consequences. In order to prevent this the thyroid of the mother and fetus is blocked by previous administration of potassium iodide (Lugol's Solution). Usually this premedication is given at least one day before injection of the tracer (10 drops t.i.d.). The radioactive decay of I^{131} occurs via emission of beta particles and γ rays and it is the former which causes the damage if taken up. The usual dose is 5 microcuries and this delivers a total maximum radioactivity of 0.02 to 0.1 rads to the fetus.¹ By comparison radiation doses from the use of X-rays have been estimated from 0.5 to 3 rads and may be as high as 10 to 15 rads with some techniques.⁹

In order to prevent even the small dosage of radiation produced by I^{131} other isotopes have been employed. Foremost among these has been chromium-51 (Cr^{51}). Cr^{51} has a half-life of 27.8 days and is a pure gamma emitter, delivering only 60 and 10 millirads to mother and fetus respectively from a 100 microcurie dose.¹ The chromium is used to tag erythrocytes and the number of erythrocytes crossing the placental barrier is negligible.¹⁰ Any isotope released during the normal physiological destruction of the blood cells by the phagocytic activity of the reticuloendothelial system is quickly cleared by the kidneys and is not available to tag other erythrocytes.¹

ACCURACY OF RESULTS

The accuracy of the technique is confirmed by subsequent caesarean section or vaginal delivery. Several

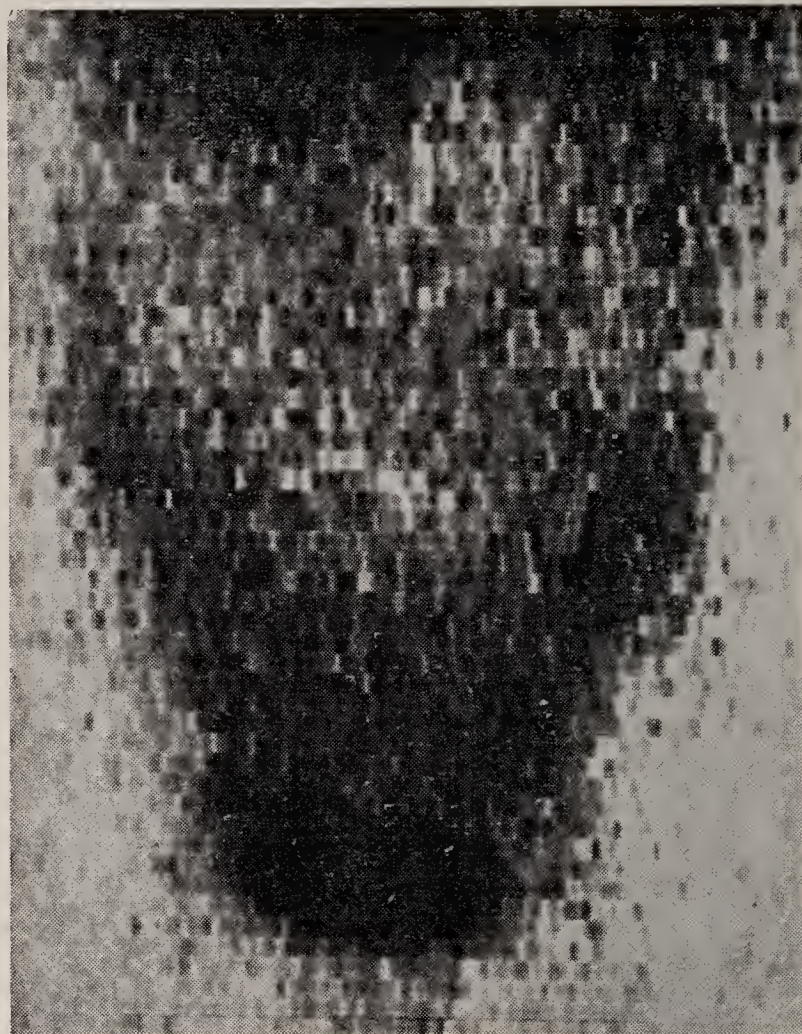


Fig. 3: Photoscan of marginal placenta previa, 32 weeks gestation. The placental blood pool lies across the lower portion of the uterus. Darkened area inferiorly shows portion of bladder.

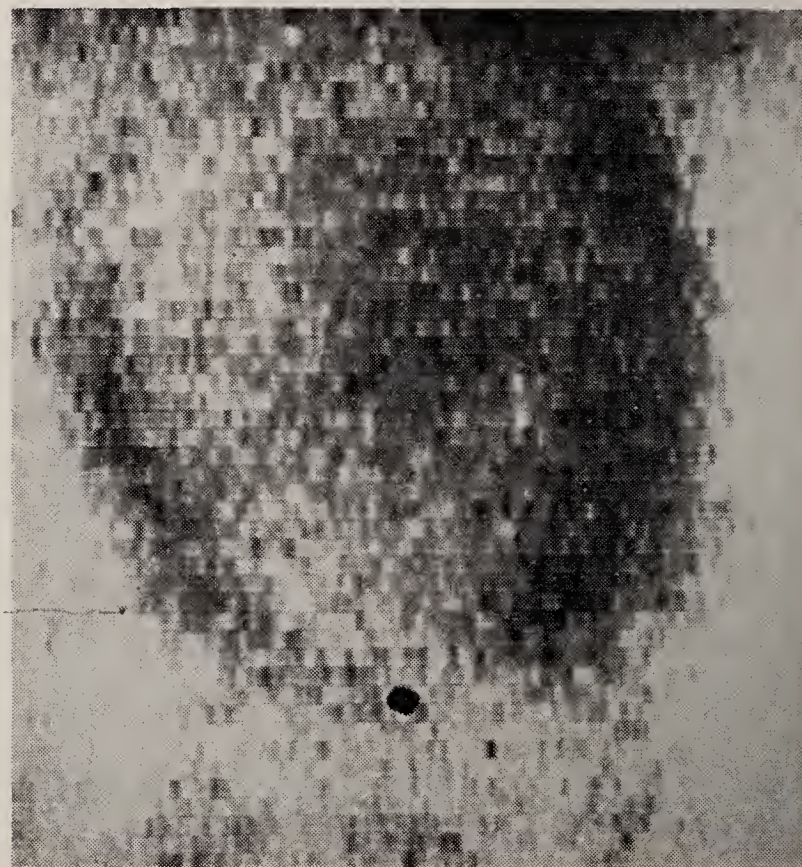


Fig. 4: Photoscan of placenta previa, 30 weeks gestation. The placenta is seen to be posterior and lateral, and the inferior margin approaches the midline (black dot at symphysis) suggesting marginal placenta previa. The patient voided just prior to photoscanning, so no radio-activity is seen in the bladder.

studies have been reported in the literature and an overall accuracy of 95% or better has consistently been achieved.^{4 7 11}

FURTHER REFINEMENTS OF TECHNIQUE

Recent advances in the field of radioisotope placentography include uterine scanning for indirect visualization of the placenta.^{5 12} One method uses technetium-99m labelled albumin. The isotope has a half-life of 6 hours and decays only by γ emission, exposing the fetus to less than 5 millirads, no preference being shown for any organ. In this technique the whole abdomen is scanned from pubic symphysis to xyphoid process and the spatial distribution of tagged albumin in the various vascular compartments is correlated with a mosaic of dots of varying intensities on a photosensitive plate. The final result is a picture corresponding to the utero-placental relationship. (Figures 3 and 4).

OTHER RADIOISOTOPE STUDIES

As a result of the experience gained in the area of placental localization investigators have tried to use radioisotopes in more varied applications. The results of intrauterine transfusion in cases of hydrops fetalis has been studied with chromium-tagged erythrocytes.¹³ It was shown that fetal ascites does not interfere with absorption of transfused cells. Spencer et al have injected RIHSA into the amniotic fluid.¹⁴ It is hoped by this technique to be able to assess the volume and distribution of the amniotic fluid, the localization of the placenta, and the fetal position after engagement.

CONCLUSION

The results obtained using isotope techniques to localize the placenta are extremely encouraging. It should be remembered however that there are great differences among people's reaction to a given dose of radiation and the decision to perform radioisotopic placentography or other radioisotopic diagnostic procedures should never be made lightly. Current research indicates that there will be an increasing number of these tests to chose from in the future.

W. Cass 6T8

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Abstract

Pulmonary Microembolism

F. W. Blaisdell et al. *Archives of Surgery* 93: 776-786. Nov. '66.

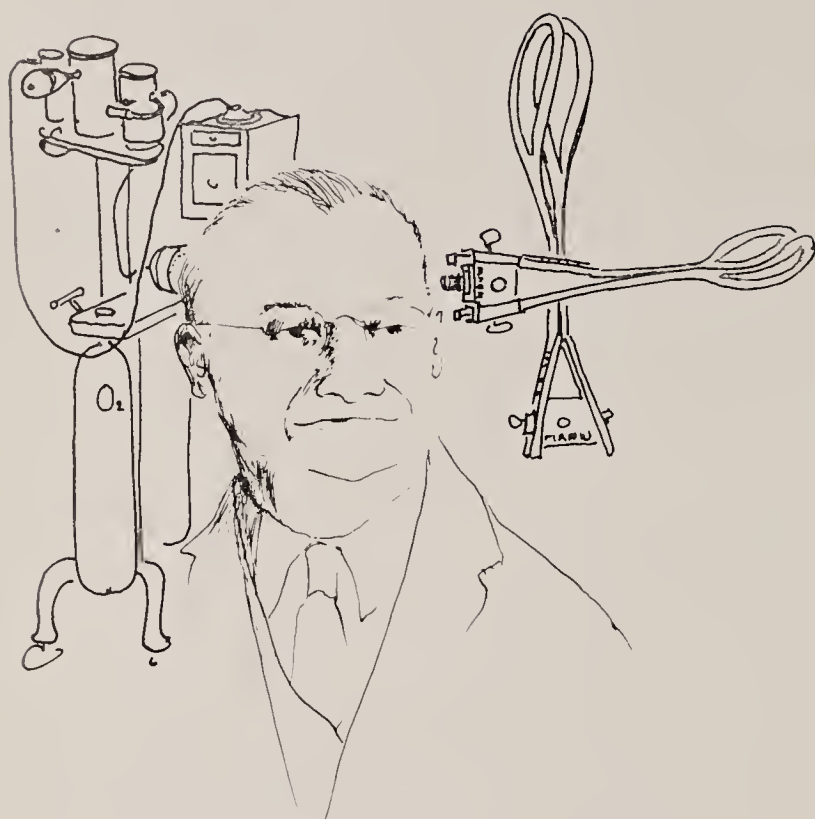
In 375 operations for aneurysms and occlusive disease of the infra-renal aorta and its branches, there were 31 deaths, 25 in the 106 emergency cases and 6 in the 269 elective operations. Eighteen of these were due to cardio-pulmonary problems and ten of these were felt to have the syndrome of pulmonary microembolism. In addition four of eight survivors from ruptured aneurysms developed serious cardiopulmonary morbidity with this syndrome.

This syndrome is characterized by: 1) local shock involving all tissues supplied by the vessels occluded during the operation; 2) a bleeding diathesis probably the result of either a depletion of the blood clotting factors due to the extensive intravascular coagulation in the local shock area or a fibrinolytic overactivity in response to the disseminated clotting in the vascular tree; 3) serious respiratory disturbances with cyanosis and arterial desaturation; and 4) manifestations of low cardiac output.

Autopsies revealed fibrin emboli in pulmonary arteries 50-200 mm in diameter in all patients who died in the first three days and none in the three patients who died five or more days following surgery. Prevention involves the avoidance of prolonged regional shock, vigorous treatment of systemic hypotension, and immediate anti-coagulation with heparin. The treatment of the syndrome involves tracheostomy, ventilation with 100% oxygen, heparinization and careful monitoring of arterial oxygen and pH.

Pulmonary microembolism may be a frequent cause of morbidity and death following emergency operation for arterial occlusive disease or ruptured aneurysm. Awareness of the cause, prevention, and treatment of this syndrome should lower the morbidity and mortality after major vascular surgery.

R.I.H.



"He was an enduring friend of the student, and over the years the debt we owe to him for the hours of instruction he gave us is heavy indeed. No hour was too late and no group too small to prevent him from sharing his knowledge on the subjects that he knew best. . . .

(With Dr. Mann's death) the last of an inspiring group of clinical teachers has departed. These men were somewhat eccentric in personality, strong in their convictions, dramatic in their methods and forceful in their presentations. What they taught you, you never forgot. Their teaching was too alive and vital, too entertaining and too fundamentally important to forget!"¹

If this description were used as a pattern today, few teachers would be found to fit this ideal. The increased demand for the product of medical schools has created a system of dispensing knowledge which is becoming increasingly depersonalized and fragmentary. Today's teachers tend to be spawned from narrowing fields of specialization. This impedes the formation of a panoramic view of the profession so necessary in the effective instructor.

Mann was born in Coatbridge, Scotland and came to Canada at the age of ten to reside in Sault Ste. Marie. His adolescent years, spent in apprenticeship training at the Algoma Steel Company in machine work, design and tool and die-making, formed the basis for his later contributions. Mann was attracted by the medical pro-

fession and attended Queen's University, mentally filing his engineering skills for future reference. After graduation in 1927, he came to the Toronto General Hospital for postgraduate training in obstetrics and gynecology. "When asked how he had come to Toronto after graduating from Queen's . . . he was accustomed to reply that obviously Toronto very badly needed a graduate from Queen's."¹ He was appointed to the staff of the Toronto General Hospital in 1930 and eventually attained the position of attending obstetrician and gynecologist and associate professor at the University of Toronto.

Mann was born a Scot and

"In true Scottish tradition he was a determined man. His was not a personality that allowed for compromise. A thing to him was right or wrong and he stood for the right as he knew it. Not only did he stand for it, but he was aggressive in its cause. In a man less friendly by nature than he, this might have contributed much in alienation. But in argument, even if you were in the wrong, he chose to overlook this on the grounds of friendship."¹

Mann had a great ability to analyze a problem, to suggest modifications in method and apparatus and to utilize his mechanical ingenuity to design efficient instruments of maximum simplicity.

Mann readily admitted that

"In larger centres where there is no shortage of interns, the interns are often employed as retractors. The additional personnel and crowding of the operative field is only one of the disadvantages of this method. In other situations where competent personnel are not so readily available or expendable, a good instrument is a good assistant."²

Mann's retractor converts a longitudinal incision into the shape of a triangle by three-point traction. When the base of the triangle is located over the operating field and a fourth adjustable retractor positioned, the maximum working space from an incision is available. Hinges, lock-nuts, screws and toothed ratchets were eliminated in its construction to prevent the irritations of torn gloves, snagged sutures and constant maintenance.

In 1953-54 Mann described a neonatal resuscitation apparatus designed to overcome the deficiencies of the popular methods. Mann believed that investigation of the airway and control of the applied pressure were necessary.

"The establishment and maintenance of a free airway is of first importance; without it no method can succeed . . . Intubation of the trachea is the only method of dealing with these situations."³

"Normally constructed alveoli expand with the inspiratory gasp at atmospheric pressure, abnormally constructed alveoli do not, and it is here that attempts to inflate the lung with higher pressures can do only damage, because the normal tissue will be destroyed before any dilatation can possibly be produced in the collapsed area."⁴

Mann's method involved intubation with an intratracheal catheter to permit suction clearing and pure oxygen administration. His apparatus consisted of a simple positive and negative resuscitation valve which delivered oxygen at fixed pressures of 12 mm Hg positive and 8 mm Hg negative. After three years of trial use at the Toronto General Hospital, Mann was confident that his technique gave the best possible chance of a successful resuscitation.

Mann showed a clear understanding of the fundamental mechanical principles involved in the construction and use of the obstetrical forceps. In 1956 he received an award from the Council of the Royal College of Obstetricians and Gynecologists for the best essay concerning the subject. After extensive analysis of previous instruments, Mann undertook the design of an improved obstetrical forceps. He and his colleagues used the instrument for over three years at the Toronto General Hospital before he described it in a 1957 paper. Mann's cautious attitude derived from his belief that "the introduction of a new method or instrument can only be justified if it is an improvement on what has gone before."⁵ His mechanically oriented mind and experience in tool design gained as an adolescent produced a truly unique device.

"The new instrument has a special lock which is split in two; each half may slide up and down on the corresponding shank. The shanks do not cross and throughout any adjustment to variations in head size the blades face parallel to each other at all times. When applied to a head in asynclitism either blade may be in advance of the other, depending on the type—anterior or posterior—or degree of asynclitism. The instrument automatically adjusts itself as the asynclitism disappears during rotation. . . . The traction handle is purposely designed as part of the lock so that rotation or traction cannot be applied until it is securely in place. The further advantage of this attachment is that when traction is applied, no com-

pression of the handles, with resulting compression of the head, can occur."⁵

Dr. Mann was an influential teacher, speaker and progressive force, not only in his field of obstetrics and gynecology but in the profession of medicine as a whole. He was a well-known and sought-after speaker and although in failing health, he accepted an invitation as guest speaker at the Detroit Academy of Medicine on November 3, 1960. It was there that Dr. John Mann died at the age of fifty-nine.

"In evaluating the various methods and instruments, it is well to remember that it is not so much the method or instrument but the man using it that counts. Whether one approves of the various manipulative procedures that have been taught does not matter, but the more one knows about other people's methods, the more efficiently and intelligently is he able to apply his own."⁵

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Editors' Note:

The drawing above portrays Dr. Mann on a background illustrating the inventive side of his genius: his forceps and his infant recussitator. But for us this picture also symbolizes that the knowledge and resources of our local medical history stand (or more precisely, wobble) on a most precarious base. Like the previous 'Medical Muses' features, the literature was examined carefully for a picture of Dr. John Mann. No published picture could be found; nor, to our great surprise, did one exist in the Department of Obstetrics and Gynecology files. Finally, after an extensive search for a picture, Mrs. John Mann was contacted, and the portrait on which the above drawing was based was rapidly forthcoming. We are extremely grateful to Mrs. Mann for providing this picture, and equally pleased that we can present this tribute to Dr. Mann. Nonetheless, it is obvious that a similar picture should have been readily available within the Faculty of Medicine. This episode, we feel, presents a prime example of the need to develop an organized, accessible archive of the people who have contributed to the growth of this faculty and the advance of medicine within it.

A.B.D. T.W.P. K.P.H.P.

The Use Of Isoxsuprine In Obstetrics

T. Picton 6T7

PREMATURE LABOUR AND NEONATAL MORTALITY

Little is known about the forces initiating the process of birth. Three factors undoubtedly play a part: the decreased inhibitory effect of placental progestins on the uterine musculature; the rising blood levels of oxytocin and the increased sensitivity of the uterus to this hormone; the distension of the uterine cavity by the maturing fetus. How important a part each of these factors play or what other factors are present—these remain unanswered questions. Without knowledge of normal physiology, one is at a loss to explain the pathology of a premature initiation of labour. Some premature deliveries may be attributed to overdistension of the uterus (multiple pregnancy, hydramnios); some are obviously due to placental factors (placenta previa, abruptio placentae); others are loosely ascribed to cardiovascular and endocrine disorders. Even the scourge of man—smoking—is invoked as a cause of premature labour. Yet the majority of premature deliveries occur in apparently normal mothers undergoing apparently normal pregnancies and bearing children whose only real defect is their prematurity. Until recently premature labour was regarded as a mysterious, dangerous but inevitable occurrence.

Mysterious as it may be, however, it remains of prime importance. Approximately 10% of pregnancies terminate prematurely (i.e. the infants weigh between 1000 gm. and 2500 gm.). These premature infants are prone to respiratory distress syndrome, hyaline membrane disease and infection; they bleed easily and withstand trauma poorly. Life takes its toll of those as yet not fully prepared for its hazards: 20% of premature infants die. Prematurity, therefore, accounts for more than half of all neonatal deaths. Even if the infant survives the neonatal period he suffers from a higher incidence of neurological and intellectual defects than infants born at maturity.² Prevention of prematurity would therefore be a tremendous advance in modern obstetrics.

THE SEARCH FOR A MYOMETRIAL DEPRESSANT

If one could depress the myometrium one might possibly be able to arrest premature labour. Many varied approaches to myometrial depression have been investigated recently. Progesterone enjoyed its vogue but control studies have indicated that this treatment has no real effect.⁸ Other centres have experimented with diazepam (Valium) and with relaxin but as yet there is no definite proof of either's efficacy. Hypothermia has been reported as successful and also hypnosis. Recently Fuchs⁹ has demonstrated that 10% ethyl alcohol given intravenously (1.25 gm./kg. given over the first hour) has striking results in the prevention of premature labour. Alcohol supposedly inhibits the secretion of oxy-

tocin by the posterior pituitary gland (one notes that alcohol also inhibits the pituitary release of vasopressin).

THE DISCOVERY OF ISOXSUPRINE

It has long been known that epinephrine causes a marked transient relaxation of the human uterus. However, the shortness of its duration and the dangerous nature of its cardiovascular side effects preclude its use as a myometrial relaxant. Isoproterenol, a beta-adrenergic agent, has fewer cardiovascular side effects but its duration is again too short. Papaverine is a direct smooth muscle relaxant but it exerts a dangerous quinidine-like effect on the heart especially when injected intravenously. In 1956 isoxsuprine (Vasodilan, Duvalilan) was synthesized. It is basically a beta-adrenergic drug analogous to isoproterenol, yet its structure also resembles that of papaverine. It was marketed with only slight success as a vasodilator. In 1960 Lish¹ showed that the drug effects a marked myometrial depression without greatly lowering the blood pressure; its duration of action seemed long enough to possibly affect the outcome of premature labour. In 1961 Bishop and Woutersz² first demonstrated its clinical effectiveness in the arresting of premature labour.

The effects of isoxsuprine are probably a combination of beta-adrenergic and papaverine-like effects.^{1 7} If labor is commencing isoxsuprine decreases both the frequency of contractions and the tone of the uterus.^{3 4 6} If labor is well advanced, however, the drug may have no effect or may even facilitate delivery—by increasing cervical dilatation and by allowing more effective contractions through decreasing the tone of the uterus.^{4 6}

THE USE OF ISOXSUPRINE IN PREMATURE LABOUR

Premature (20-36 weeks) labour may present with one or more of the following signs: uterine contractions, bloody show, cervical dilatation, ruptured membranes. Significant bleeding is a definite contraindication for isoxsuprine therapy since the cardiovascular effects of the drug will only mask the clinical picture of a placenta previa or an abruptio placentae. The drug has been found to be ineffective if the cervical dilatation has exceeded 4 cm. or if the membranes have ruptured. However, with a patient in premature labour with intact membranes, no bleeding and cervical dilatation of less than 4 cm. isoxsuprine should be given immediately by intravenous infusion.^{2 5} It may be given at the rate of 0.25-0.5 mg./min. (40-80 mg. in 500 c.c. of 5% dextrose in water) for up to three hours. The patient should be lying on her side to prevent pooling of blood in the lower extremities; the blood pressure must be frequently monitored. Then 10-20 mg. may be given intramuscularly every three hours over the first day; after that the patient may be started on a similar oral dose which may gradually be decreased to a maintenance dose of 10 mg. four times a day.

THE USE OF ISOXSUPRINE IN OBSTETRICS

If after the intravenous infusion of the drug the uterus does not quiet down and labour continues to progress, it is probably advisable to discontinue treatment. Otherwise one might run into the problems of uterine inertia or of postpartum hemorrhage.¹⁰ The patient should be prepared for labour. The four principles of management in premature labour should be enforced: no analgesics, no anesthesia other than regional anesthetics, liberal episiotomy, spontaneous delivery by gentle fundal pressure. It is also suggested that oxygen be given to the mother to aid fetal oxygenation, that the cord be clamped early to alleviate any infant hemolytic disease, and that oxytocics be given after delivery to prevent postpartum hemorrhage.

The results of the drug, however, are usually quite striking.^{3,4,5} Labour is arrested long enough (sometimes up to four months) for the infant to be born at maturity in over 40% of treated cases. Labour is temporarily arrested in 35% of the cases and no effect is noted in the remaining 25%. Accurate control studies are sadly lacking, but the most that one could expect with similarly selected patients would be that 15% might possibly carry to maturity without treatment.⁸

The major side effects of the drug are due to its beta-adrenergic effects on the cardiovascular system.^{2,3,5,6} Tachycardia and mild hypotension are noted in most patients; a fall in blood pressure of more than 20 mm., however, is noted in only 2% of cases. No significant effects on the fetus have been recorded. Other less important side effects include nausea, vomiting, headache, dizziness, drowsiness, shivering, and sweating.

OTHER OBSTETRICAL USES OF ISOXSUPRINE

Karim⁴ has used isoxsuprine for many other obstetrical problems. It seems to be effective in arresting a threatened abortion (3-5 months); it has also been used to supplement the Shirodkar operation for "incompetent cervix" in habitual abortion. He has used isoxsuprine as an aid in neglected complex presentations: the drug allows for sufficient relaxation of the uterus to complete podalic version in shoulder presentations; it may release a contraction ring facilitating the insertion of forceps for delivery. The drug is an aid to the replacement of an inverted uterus. It is possible that isoxsuprine might be effective in the management of dystocia due to hypertonic uterine dysfunction.

FUTURE POSSIBILITIES

Research continues. At present it is essential that a properly controlled double blind study be done to demonstrate clearly the efficacy of the drug and to provide a baseline for the study of similar drugs. It is claimed that certain methanesulfonamide derivatives of isoxsuprine may be more effective than the original drug.⁷ The use of beta-adrenergic blockers such as propranolol^{1,7} may allow the injection of higher doses of isoxsuprine without fear of the cardiovascular consequences. Landesman⁷ suggests the possible combined

use of ethyl alcohol, isoxsuprine and a beta-adrenergic blocker in the treatment of premature labour. Isoxsuprine and its derivatives have many possibilities—combined with the oxytocics they may well represent the key to medical control over the initiation of labour.

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Genetic Counselling

D. Palframan

A) INTRODUCTION

When a couple give birth to a malformed baby, they want to know what the probability is that subsequent children will be similarly affected. The total incidence of malformations of clinical significance is in the general order of two or three percent.¹ When the host of serious diseases with a powerful genetic etiologic factor is added to this two or three per cent of live births, the magnitude of potential situations where genetic counseling may be sought becomes enormous. After a malformed baby has been born, genetic counseling is already after the fact. The detection of heterozygous carriers will allow carrier couples to approach child-bearing with the information necessary to prevent or mitigate the painful guilt complexes and horrified shock felt by the parents of a malformed baby. Perhaps ultimately, the prevention of harmful malformations will become a clearly defined public health discipline.²

B) DETECTION OF HETEROZYGOUS CARRIERS

A prognosis in genetic counseling can be given with much more accuracy if the carrier status of the prospective parents is known. In the dysproteinemias and hemoglobinopathies, carrier status is readily detected by relatively simple examinations of the plasma proteins and red blood cells respectively. However, most genetically determined disease states are more difficult to detect carrier status. In general, the value for a particular enzyme or metabolite activity is found to be intermediate between that of the affected homozygote and the unaffected homogygote. There are many very rare conditions that can be so detected, and a very few less rare ones.

(i) *Wilson's Disease*—A method for detecting carriers of Wilson's hepato-lenticular degeneration depends on their decreased caeruloplasmin level. Cu^{64} incorporation into caeruloplasmin is measured. Unfortunately, the values obtained in control subjects vary with age, and so accurate discrimination of carriers is not possible.³

(ii) *Gargoylism*—Hurler's syndrome carriers are suspected of having increased polymorphonuclear segmentation. However, the data from parents of affected children overlap with those from normal adults.⁴ There have been unsuccessful attempts to show either qualitative or quantitative differences in the excretion of mucopolysaccharides between normals and the parents or siblings of patients.⁵

(iii) *Phenylketonuria*—Carriers of the recessive gene for phenylketonuria have a reduced capacity for oxidizing a loading dose of phenylalanine. Here again, there is overlap with control data.

(iv) *Acatlasia*—Carriers of the gene for this condition, which causes oral gangrene, are detected by a clear distinction between affected homozygotes, heterozygotes and non-affected homogygotes in blood catalase activity.

(v) *Pseudocholinesterase Deficiency*—Presumed carriers do not show a prolonged apneic response to succinyl choline, but do have a slightly lower than normal serum pseudocholinesterase activity.

(vi) *Duchenne's Muscular Dystrophy*—Perhaps the most valuable clinical use of tests for heterozygote carriers is in the detection of carriers of Duchenne's childhood muscular dystrophy. Inheritance is by an x-linked recessive pattern and a suspected carrier female should have plasma aldolase or urinary creatine phosphokinase determinations done. Most carriers show a significant elevation of one or both enzymes. Those who prove to be carriers by having affected children, yet have no enzyme elevation are thought to be mutants, or else the affected children are thought to be phenocopies of the genetic disease.⁶

(vii) *Leukemia*—A clue to the elucidation of leukemias may prove to be the as yet unexplained finding of hemoglobin H (a B_4 globulin chain) in some patients with this type of disease, and in their parents.⁷

Two of the more important failures in carrier detection are cystic fibrosis of the pancreas, and Huntington's chorea. In cystic fibrosis, sweat electrolyte tests for carriers have proven unreliable. In Huntington's chorea, the presence of the dominant gene is indicated only by clinical manifestations of the disease, occurring often after the patient's children have become parents, thus passing on the lethal trait to 50% of their children.

In summary there are useful methods for the detection of the carrier state in the hemoglobinopathies and dysproteinemias, Wilson's disease, acatalasia, pseudocholinesterase deficiency, and Duchenne's muscular dystrophy.

C) COUNSELING

Genetic counseling depends on an understanding of basic laws of genetic transmission, and on a knowledge of the prognosis and course of hereditary diseases. If a

GENETIC COUNSELLING

definite pattern of inheritance is known, then there is usually a known statistical probability of the affliction of a subsequent child. "In other cases, genetics is obviously involved, but no definite pattern of inheritance can be demonstrated, so precise advice is impossible to give. There is often a known empiric risk that any succeeding child will have the abnormality." ⁸

The physician must realize that every couple has a right to have children even with the most forbidding of genetic prognoses. It is his duty to supply the prospective parents with statistical probabilities, couched in meaningful terms, and with information about the other factors involved. Some of the factors in the personal acceptance of genetic counseling are the seriousness of the potential defect; whether it is acutely fatal, or chronic and progressive; the cost of treatment, and the economic status of the family; and the presence or absence of other healthy children.

Before the physician offers his information and tacit advice, he should explore the family tree of his patients for evidence suggestive of chromosomal anomalies. He may find outright examples of similar conditions in relatives, a high frequency of abortions or still-births, infertility, leukemia, mental retardation or mosaicism (heterochromia iridis).

D) STATISTICAL INFORMATION

The twenty most common causes for counseling at the Dight Institute⁹ are:

- | | |
|------------------------------------|------------------------------------|
| 1. Skin Colour | 11. Spina Bifida and Hydrocephalus |
| 2. Epilepsy | 12. Huntington's Chorea |
| 3. Consanguinity | 13. Diabetes |
| 4. Mental Deficiency and Mongolism | 14. Albinism |
| 5. Schizophrenia | 15. Allergies |
| 6. Hare-lip and Cleft Palate | 16. Hemophilia |
| 7. Eye Colour | 17. Paternity Determination |
| 8. Twinning | 18. Manic-depressive Psychosis |
| 9. Rh Factors | 19. Mucoviscidosis |
| 10. Cancer | 20. Sterility |

Please note that this list represents not the frequency of these conditions, but the interests of the public. Genetics becomes intermixed with social problems in questions of the skin colour and paternity determination. The geneticist should deal in safe and reliable statistics, but the physician must be always aware of the social implications of his genetic counseling.

The statistics to follow include some conditions that are not commonly thought of as having genetic determination. In each condition, a genetic determinant has been proven by comparison of studies of fraternal twins and of identical twins. The twin studies showed a statistically significant higher incidence of the condition if

the twin of the patient was identical, than when the twin was fraternal.

(i) *Mongolism*

Mother's Age	20 - 30	40 - 50
Risk first child will be a mongol	4 in 10,000	250 in 10,000
Risk for next child with one mongol	12 in 10,000	600 in 10,000

(ii) *Central Nervous System Malformations*—The figures are restricted to the serious malformations, especially hydrocephalus, anencephaly, and spina bifida.

60 of 10,000 of viable births are affected, as well as 3 per cent of subsequent siblings. Also, after an affected child has been born, the rate of spontaneous abortions and still birth rises to 20 per cent. Thus, the total rate of loss or malformation in subsequent siblings is 23 per cent, or nearly one in four pregnancies.

(iii) *Severe Non-Specific Mental Retardation*

50 - 100 in 10,000 of all births are so affected.

Probability for next child

One sibling and neither parent affected	300 - 1500 in 10,000
One sibling and one parent affected	4000 in 10,000
One sibling and both parents affected	9000 in 10,000
One parent affected	3000 in 10,000

Care must be taken to exclude conditions such as Tay-Sach's disease, where the probability for each child is 25%.

(iv) *Hare-lip and Cleft Palate*—The incidence of either or both deformities in the general population is 13 in 10,000. Since cleft palate alone has a different genetic basis from cleft lip with cleft palate or cleft lip alone, the statistics for cleft palate will be presented separately.

a) CLEFT LIP AND PALATE

Probability for Next Child

One sibling and neither parent affected	500 - 1400 in 10,000
One sibling and one parent affected	1100 in 10,000
One parent affected	200 ¹⁰ or 1700 ¹¹ in 10,000

b) CLEFT PALATE

Probability for Next Child

One sibling and neither parent affected	200 - 500 in 10,000
One sibling and one parent affected	1500 in 10,000
One parent affected	700 in 10,000

(v) *Club Foot*—The frequency in the general population is 10 per 10,000. The frequency in siblings of af-

affected children is 300-800 per 10,000, and if one parent is affected, 1,000 per 10,000.

(vi) *Epilepsy*—The frequency of idiopathic epilepsy in the general population is 40 in 10,000. If one parent is affected, there is a 2.5 - 5% chance that the child will have a seizure, but only a 1.4% probability that the seizures will persist into adulthood.

Lennox, Gibbs and Gibbs¹¹ did a classic study in 1939 of the E.E.G. recordings of 140 epileptics, as well as their parents and near relatives. 81% of the epileptics had one or both parents with an abnormal cerebral arrhythmia, and 50% of the near relatives showed a similar arrhythmia. Their conclusion was that this was a hereditary arrhythmia which would produce epilepsy when the brain was injured, and without which a more serious injury would be necessary to produce epilepsy. More recent information on the correlation between minor sub-arachnoid haemorrhages and momentary anoxic episodes during labour, leading to subsequent "idiopathic" epilepsy and hydrocephalus, may bear out this hypothesis.

(vii) *Diabetes Mellitus*—The frequency of diagnosed diabetics in the general population is slightly over 100 per 10,000. It is estimated that the total frequency of diabetics — diagnosed, undiagnosed and potential — is 500 per 10,000.

Probability for next child		
	by age 20	by age 70
One sibling and neither parent affected	500 in 10,000	1,000 in 10,000
One parent affected	500 - 1500 in 10,000	

Pincus and White have projected their statistics and say that if the siblings of a diabetic were to live to age 90, 25% of them would have diabetes by that time.¹²

(viii) *Congenital Heart Disease*—The frequency in the general population is 36 per 10,000. If one child is affected, the risk for subsequent children is 180 per 10,000 but, the risk of some significant abnormality, not necessarily in the heart, is 50%.

(ix) *Rheumatic Fever*—The frequency in the general population is 46 per 10,000, with the frequency rising to 300 per 10,000 in epidemics.

Probability for next child		
	Concurrently	Eventually
One sibling and neither parent affected	460 in 10,000	900 in 10,000
One parent affected	950 in 10,000	1900 in 10,000

(x) *Mucoviscidosis*—This is a recessive gene trait, and affects 25% of the children if both parents are heterozygotes.

(xi) *Pyloric Stenosis*—This condition occurs in 30 per 10,000 live births, and 80% of those affected are male.

Of subsequent children, 2% of the females and 10% of the males will be affected.

(xii) *Congenital Dislocation of The Hip*—The frequency of female babies affected is 20-50 per 10,000—ten times the frequency in males, due to the shallower acetabulum in the female pelvis. If a parent was affected, then 10-15% of the siblings of an affected child will be affected. With neither parent affected, 5% of the siblings of an affected child will have a congenitally dislocated hip.

(xiii) *Allergies*—About 10% of the general population have hay fever, migraine, asthma or urticaria. 20% of the children of these parents will have one of these conditions.

(xiv) *Schizophrenia*—1-5% of the general population suffer from schizophrenia during their life-time.

Probability for next child	
One child affected	1,000 - 1,400 in 10,000
One parent affected	1,800 in 10,000
Both parents affected	50%

E) CONSANGUINITY

In the event that related people wish to marry, they should be made aware of the statistical risks their consanguinity confers on their off-spring. The couple have an increased possibility of bringing together two identical recessive genes, and so allow an undesirable trait to be expressed. Also, traits produced by polygenic inheritance have an increased rate of occurrence in consanguineous marriages. A W.H.O. report in 1964 showed the death rate of children from consanguineous marriages to be 810 per 10,000 by age 10, compared to 240 per 10,000 by age 10 in a control group. Thus, first cousins, contemplating marriage must realize that they are tripling their children's chances of being born with a serious hereditary defect or a hereditary susceptibility to a serious disease.

The incidence of club foot in the siblings of affected children rises from 3 - 8% to 27% with consanguinity. In Tay-Sachs amaurotic idiocy, 25% of those affected come from marriages of first cousins. 10% of those with Friedreich's ataxia come from first cousin marriages. There are many other conditions where the risk of occurrence is much increased by consanguinity.

F) EUGENICS

Thwarting, by medical means, the methods by which natural selection keeps deleterious gene frequencies at a low level, leads to an increase in the frequency of the deleterious gene. If selection is relaxed so that a genetically unfit gene becomes able to express itself through a normal life span, then this gene, helped by mutation pressure, will expand over the generations. The preservation of the genetically unfit is a subject of

GENETIC COUNSELLING

considerable debate, but no one seriously recommends withdrawal of medical aid from those who need it because of the dysgenic affect of such aid. However, there is debate as to whether genetically handicapped persons should be allowed to reproduce, or encouraged to limit their reproduction.¹³ Eugenics laws, so-called, often require sterilization of people who are genetically fit, but sociologically undesirable. Even if a particular group could be selected for sterilization, mutations and the continued procreation of undiagnosed members of the group would prevent any significant eugenic effect.

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Shock In An Obstetrical Patient

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CASE PRESENTATION

A 36 year old para I, gravida III woman was admitted to hospital in active labour 28 days after her expected date of confinement. Her antenatal course was uneventful. She was first seen in the prenatal clinic at nine weeks gestation at which time physical examination was unremarkable. Pelvic assessment revealed an adequate gynecoid pelvis. Prophylactic iron therapy was maintained throughout pregnancy and the hemoglobin remained above 11.5 gm. There was no vaginal bleeding or abdominal pain at any time. The total weight gain was 25 lb. Her past health was non-contributory. The obstetrical history included vaginal delivery of a 7½ lb. boy, 12 years previously following a normal pregnancy and labour. In addition, the patient had a first trimester spontaneous abortion 6 years before her present pregnancy. The past medical and surgical history was negative except for a tonsilectomy and appendectomy in childhood. There was no history of allergies or drug sensitivities.

On admission to hospital at 10:00 p.m. physical examination revealed a slightly obese white female in mild distress. She was having moderately strong, 25 second contractions occurring every 6-7 minutes; the cervix was well effaced and 4 cm. dilated. The blood pressure was 140/80. The foetus was presenting as a left occiput anterior at the spines. The foetal heart was 140/min. and regular. Labour proceeded normally and the patient was adequately sedated initially with Secobarbital (Seconal) 0.2 gm. At 3:00 a.m., 5 hours after admission, her membranes ruptured spontaneously and labour became more active. She became quite distressed and was given Promethazine (Phenergan) 25 mg. and Meperidine 150 mg. (Demerol). By 4:00 a.m. she was fully dilated, the head was in midpelvis, and the patient was taken to the delivery room where an epidural anesthetic was administered. At 4:30 a.m. amniotic fluid was noted to be meconium stained. The foetal heart had dropped to 90/min. and it was therefore decided to deliver her as quickly as possible. After a midline episiotomy a midforceps extraction was performed. Despite these measures, a stillborn female was delivered with the cord wrapped tightly around her neck. Attempts at resuscitation for one hour were unsuccessful.

Following delivery the patient appeared normal. The placenta separated without difficulty and was delivered. There was no undue bleeding and the episiotomy was sutured. The blood pressure was 135/85. Fifteen min-

utes later at 5:00 a.m. the patient suddenly became confused and disoriented. Her blood pressure was 80/40 and the pulse 120. Respirations were laboured and slight bleeding from the vagina was noticed. The uterine fundus was located at the umbilicus and was firm. Blood was sent for crossmatching and an intravenous was started (500 cc. of 5% glucose in water to which 10 cc. of Oxytocin (Syntocinon) was added). The total external blood loss was estimated at 1000 cc. Obstetrical consultation was requested and obtained in 15 minutes.

DIFFERENTIAL DIAGNOSIS

With the sudden onset of shock, a differential diagnosis must be considered. Dr. John Whiteside, of the Department of Obstetrics and Gynecology, Toronto General Hospital, will present a differential diagnosis of postpartum obstetrical shock, with particular reference to the case.

DR. WHITESIDE:

When faced with the sudden onset of shock in the immediate postpartum period, as illustrated in this case, four general etiological factors must be considered. The first, and most common, is hypovolemic shock due to blood loss. Postpartum hemorrhage is defined as blood loss in excess of 500 cc. occurring anytime from the birth of the infant to the end of the puerperium. The patient has lost only 1000 cc. of blood vaginally and, while this is by definition a postpartum hemorrhage, this amount of blood loss is unlikely to produce the degree of shock seen here. It is, however, entirely possible that hemorrhage is continuing unrevealed into the broad ligaments or peritoneal cavity as a result of one or more uterine lacerations. An immediate and careful exploration of the uterine cavity must be made to rule this out. Uterine atony, the commonest cause of postpartum hemorrhage, seems unlikely in this case for two reasons. Firstly, we are told that the fundus was firm and well descended following delivery, and secondly, hemorrhage from this cause in the absence of lacerations occurs vaginally and would thus be revealed. I assume that the placenta and membranes were found to be intact and that we can therefore rule out retention of placental parts as a cause of the vaginal bleeding. Secondly, does this case represent sensitivity to a drug or to anesthesia? There is no history of the former but it remains a possibility. Or was there systemic absorption of a local anesthetic agent? Peripheral vaso-

dilatation following the absorption of epidural anesthetic, combined with 1000 cc. of blood loss, could lead to this type of clinical picture. As this case is presented, there is nothing to suggest or support bacteremic shock as an etiological factor. The sudden onset of the shock with no history of fever, chills, flushed cheeks and so on, renders this a doubtful diagnosis. Finally, has she an amniotic fluid or air embolism? This, I suppose, is a diagnosis of exclusion but could well account for her hypotension, tachycardia and dyspnoea. Certainly, in a 36 year old multipara, supposedly 4 weeks past term, provided that pelvic examination reveals no lacerations, this diagnosis must be suspected.

Bimanual pelvic examination revealed a well contracted uterus in which no uterine lacerations were found. One small vaginal tear was disclosed which was felt to be the source of the continued bleeding. This was sutured and bleeding ceased. Two tiny paraurethral lacerations were still oozing slightly but did not merit closure. During the next hour the patient's condition did not improve despite a firm uterus and absence of overt bleeding. She remained shocked (blood pressure 75/40) with continuing moderate dyspnoea. At 6:15 a.m. a venous cutdown was performed and whole blood was administered rapidly. She was also given Hydrocortisone (Solu-Cortef) 300 mgm. intravenously. There was no response. A clot observation test revealed total absence of clotting of the patient's blood after 10 minutes. The fibrinogen level was not obtained. The patient continued to deteriorate and at 7:30 a.m. respirations ceased and the blood pressure disappeared. Artificial respiration and external cardiac massage were to no avail and the patient was pronounced dead at 8:05 a.m.

AUTOPSY FINDINGS

The only significant findings were in the lungs and uterus.

Uterus

Squames were found in the uterine veins in great numbers. Otherwise a normal postpartum uterus and cervix were revealed.

Lungs

Numerous squames and the occasional lanugo hair were seen in many capillaries in both lungs. Meconium stained mucinous material was also noted (Figs. 1 and 2). Grossly, the lungs revealed massive congestion and pulmonary edema. The right lung weighed 680 gm. (normal 450 gm.) and the left 400 gm. (normal 375 gm.) There was some degree of atelectasis in both lower lobes and multiple hemorrhages were present in both lungs.

The autopsy findings were otherwise normal. No clotting was present in the systemic circulatory system.

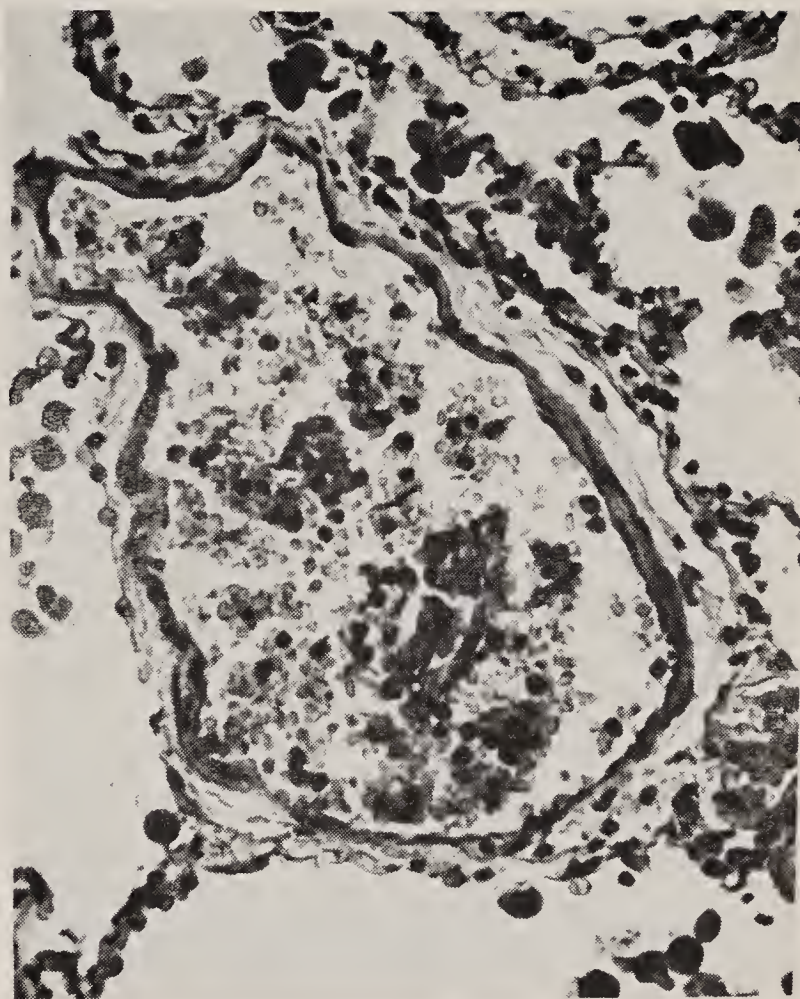


FIG. 1: X-section of pulmonary capillary showing squames which appear as elongated, darkened objects to the left of centre in the capillary.



FIG. 2: Another pulmonary capillary showing squames and meconium-stained mucin in the upper right portion of the capillary.

ANATOMICAL DIAGNOSES

1. Massive particulate amniotic fluid embolism.
2. Acute right heart failure with acute passive congestion of the lungs and pulmonary edema.
3. Pulmonary hemorrhages secondary to
 - ? acute right heart failure
 - ? hypofibrinogenemia

DISCUSSION

I. GENERAL CONSIDERATIONS

Amniotic fluid embolism occurs when amniotic fluid, and the particulate constituents of the fluid, gain access to the maternal venous system. The most common mechanism involves leakage through a defect in the membranes by which the fluid dissects around behind the membranes to enter the maternal circulation through large venous sinusoids located at the placental site. The defect may occur prior to rupture of the membranes but it is much more likely following rupture, whether it be spontaneous or induced. Less common mechanisms include uterine rupture, Caesarian section, and rarely, placental defects. Amniotic fluid embolism has also been associated with abruptio placentae.

II. INCIDENCE

The phenomenon is not as rare as commonly thought since evidence of embolism has often been found in the lungs of postpartum women, dead of other causes. However, as an obstetrical complication it is rare, with the incidence variously estimated between 1 in 14,000 births and 1 in 37,000 births. Statistically, there are several predisposing factors. The women tend to be older, white multiparas. Labour usually occurs at term or often past term and it tends to be either difficult and prolonged or rapid and tumultuous. The prevalence of induction or stimulation of labour with oxytocics is disproportionately high. This is not to suggest that oxytocics cause amniotic fluid embolism, but that precipitate labour caused by their indiscriminate use may be followed by the condition. Interestingly, there is a high incidence of stillbirths in cases of amniotic fluid embolism.

III. SYMPTOMS AND SIGNS

The clinical course of the condition may be considered in three stages.

Stage 1. This stage is marked by the sudden onset of shock accompanied by right heart failure. It may begin without warning or be heralded by confusion, anxiety or vomiting. The onset usually occurs during labour or the first few hours afterwards, and is most frequent at the end of the first stage. Diagnostically, a sudden fall in blood pressure and a rapid weak pulse accompanied by dyspnoea, cyanosis, acute pulmonary edema and jugular venous distension should make one suspicious

of amniotic fluid embolism. It is important to realize that pulmonary edema in this condition results, not from left heart failure, but from blockage in the pulmonary circuit as will be explained shortly. X-rays may reveal acute dilatation of the right heart and mottled perihilar infiltration bilaterally. Electrocardiography will usually show right heart strain.

Stage 2. Later in the course of the condition, if the patient survives, a hemorrhagic diathesis occurs. This is commonly manifested by profuse postpartum bleeding, despite a firm uterus and absence of lacerations. The bleeding tendency is, however, widespread and may be revealed in other organ systems than the genital tract.

Stage 3. This stage is characterized by acute renal shutdown and anuria.

IV. PROGNOSIS

The prognosis in amniotic fluid embolism is extremely grave and death usually results in a very few hours. The prognosis improves with the duration of the condition and the few reported cases of survival have occurred when the patient has reached the third stage.

V. ETIOLOGY AND PATHOGENESIS

The etiology of amniotic fluid embolism is clearly the infusion of amniotic fluid containing particulate matter into the maternal circulation. However, the pathogenesis remains very much unsettled. It is convenient to consider this matter in terms of the clinical stages.

Stage 1. In this situation one seeks to explain how amniotic fluid in the arterioles and capillaries of the lungs causes right heart failure and shock. In this regard there are currently three theories held.

The particulate theory holds that disseminated emboli in the lungs result in mechanical blockage of the pulmonary circuit. Thus, acute pulmonary hypertension develops with resultant right heart dilatation, failure and shock. Other investigators have modified this theory somewhat, since the quantity of particulate matter found in the lungs at autopsy is often insufficient to explain the degree of heart failure on the basis of mechanical blockage alone. They have postulated a reflex vascular spasm or an allergic (anaphylactic) reaction to foreign proteins in the amniotic fluid.

The thromboplastin theory states that the exciting factor is not particulate matter but thromboplastin in the amniotic fluid. Increased thromboplastin activity in the maternal circulation leads to intravascular clotting in which large amounts of fibrinogen are converted to fibrin. Fibrin emboli then lodge in the pulmonary vessels resulting in acute pulmonary hypertension. This theory has also been offered to explain the second stage as will be discussed, but objections have been raised because amniotic fluid does not contain large amounts of thromboplastin, fibrin emboli in large numbers have

never been identified, and in animal experiments, filtered amniotic fluid does not result in shock.

A third theory has been postulated by some investigators who feel that platelet thrombi seen in the pulmonary vessels are responsible for mechanical blockage. Others have suggested that in addition, the damaged platelets release serotonin which causes further pulmonary vasoconstriction. It is not known whether the formation of the thrombi is in response to thromboplastin or particles in the amniotic fluid.

Stage 2. The pathogenesis of the hemorrhagic diathesis that follows the shock is equally controversial. It has been found that many clotting factors besides fibrinogen are decreased; one explanation for this is again, the thromboplastin theory. The state of hypercoagulability that results, uses up clotting factors leading to uncontrolled hemorrhaging. Other investigators however, have found a plasminogen activator in the blood of patients with amniotic fluid embolism, and thus ascribe the bleeding to increased fibrinolytic activity. A third possibility is that when platelet thrombi are formed in the lungs, damaged platelets release a factor which accelerates the formation of plasma thromboplastin. A fourth theory postulates that as a result of shock in the first stage mast cells release heparin into the blood which acts to inhibit the clotting mechanism at all levels.

Stage 3. Shock results in decreased perfusion of the kidneys and the resulting renal ischemia leads to acute tubular necrosis and anuria.

VI. PATHOLOGY

The findings at autopsy are often quite unremarkable considering the total collapse and rapid death that usually result. The diagnosis depends upon the presence of amniotic debris in the arterioles and capillaries of the lungs. This may include squames (desquamated foetal epithelial cells), meconium, lanugo hairs and mucin. These may occasionally be seen in the uterine veins as well. Pulmonary congestion and pronounced pulmonary edema are usually present. If the patient has died during the hemorrhagic diathesis of the second stage, multiple hemorrhages may be found in virtually any organ system.

VII. TREATMENT

The initial treatment of amniotic fluid embolism is directed toward relieving the acute pulmonary edema; leaving in mind that in this condition pulmonary edema results from pulmonary vasospasm and that heart failure is secondary to the acute right ventricular load and myocardial anoxia.

Thus, treatment of the first stage may include morphine, oxygen, aminophylline, digitalis and, Isuprel. Methods of reducing the blood volume such as diuretics, tourniquets and phlebotomy must be used with caution since these patients have often lost blood in the first place. One additional therapeutic measure advised by most authorities is the administration of Atropine 0.4 mg. Subcutaneously, repeated as indicated. Atropine is employed to ease reflex vasospasm in the pulmonary vessels.

Massive hemorrhage during the second stage of amniotic fluid embolism is largely preventable. It is suggested that whenever confusion, or other signs indicating the possible onset of shock are noted, a clot observation test and fibrinogen level be done immediately. The indication for these is obvious once right heart failure and respiratory distress have developed. Hypofibrinogenemia is treated with Fibrinogen 2 gm. intravenously in repeated doses (usually 4 gm. is sufficient to prevent hemorrhage). If hemorrhage does develop, blood should be administered rapidly of course, but extreme caution should be taken not to overload the circulation and worsen the pulmonary complications. In this regard central venous pressure monitoring is helpful.

Several additional measures, while not standard therapy, have been proposed by some authorities. Those who feel that widespread intravascular clotting precipitates a hemorrhagic diathesis recommend the use of heparin to prevent this. Others, feeling that fibrinolysis is responsible, advocate the use of fibrinolytic inhibitors such as Epsilon-Amino Caproic Acid (EACA) and Trasylol.

It is to be hoped that further experimental work in the near future will resolve much of the present confusion surrounding the pathogenesis and treatment of amniotic fluid embolism.

ACKNOWLEDGMENT

I wish to thank Dr. John Whiteside, of the Department of Obstetrics and Gynecology, Toronto General Hospital, for his kind assistance in the preparation and discussion of this case.

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Eponyms And The Men

So often it is in our medical endeavours that we describe a sign, test, or procedure by its obscure eponym, the more obscure the more impressive, a suitable hypothetical example being Doltzbunger's sign. Less often does an astute colleague ask, "Who was D.....?" to which the frequent facile reply comes, "D..... was a famous surgeon (or obstetrician, or dermatologist, etc., as the occasion calls) at the turn of the century" . . . the century not specified. For reasons of precision the fashion now is to describe by definition rather than by eponym. Some eponyms, however, have resisted extinction mainly because they mentally epitomize processes lengthy to describe. But eponyms originally served a second purpose as well, that of commemorating the physicians who discovered, employed, and first taught the eponymized processes or principles. As a short reminder that *there actually were men behind eponyms*, some capsule comments on a few noted obstetrical eponymes follow.

WILLIAM SMELLIE (1697-1763) of forceps and Smellie-Veit-Moriseau manoeuvre fame, introduced the steel-lock forceps, the curved and double-curved forceps, and wrote the first book discussing the safe rules for the use of forceps 'Midwifery' (1752). Among his pupils was WILLIAM HUNTER who first demonstrated that the maternal and fetal circulations were separate.

JOHN BRAXTON HICKS (1825-1897) was a well-known obstetrician and lecturer in London. Besides the contractions and the method of version which bear his name, he wrote on concealed uterine haemorrhage, and the uterus in obstructed labour.

CARL SIGMUND FRANZ CREDE (1819-1892) of Berlin and later Leipzig is best known for his now rarely used method of external manual expression of the placenta (1860). However, every baby is directly affected by his work, for it was Credé (1884) who first instilled 1% silver nitrate solution into the eyes of newborns' to prevent gonorrheal conjunctivitis.

FREDRICH TREDELENBURG (1844-1924), also of Berlin and Leipzig is recognized for the position used in pelvic surgery, the gluteal gait and the sign in congenital hip dislocation. His accomplishments include founding the German Surgical Society and pioneering the surgery of tracheal stricture, and gastrostomy for esophageal stricture. Trendelenburg was the first to attempt operation for pulmonary embolus (1908), a feat first successfully performed by his pupil KIRSCHNER (1924).

K.P.H.P.

Reference: Garrison, F. H.: History of Medicine, 4th edition 1929, reprinted 1961. W. B. Saunders Co. 1961.

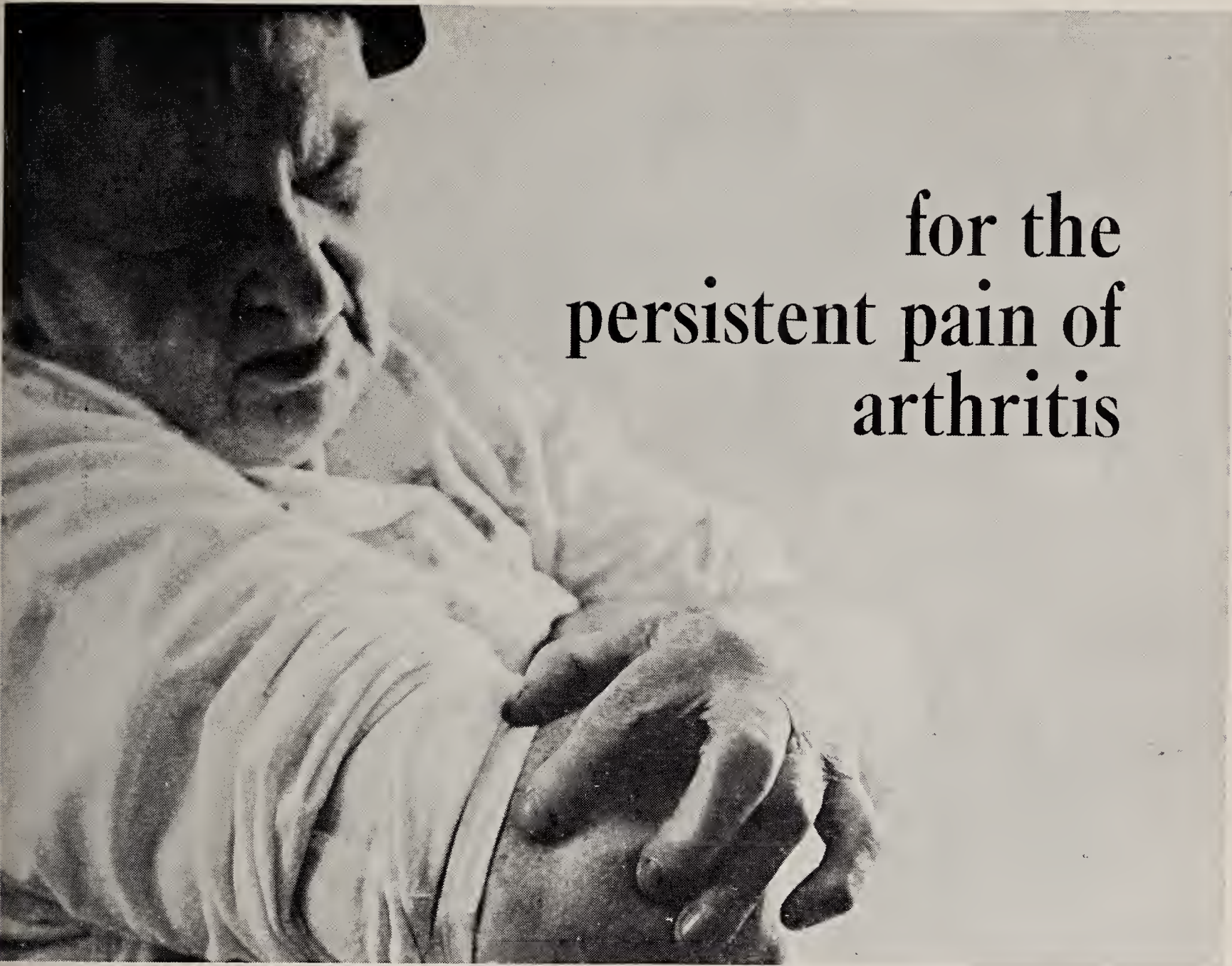
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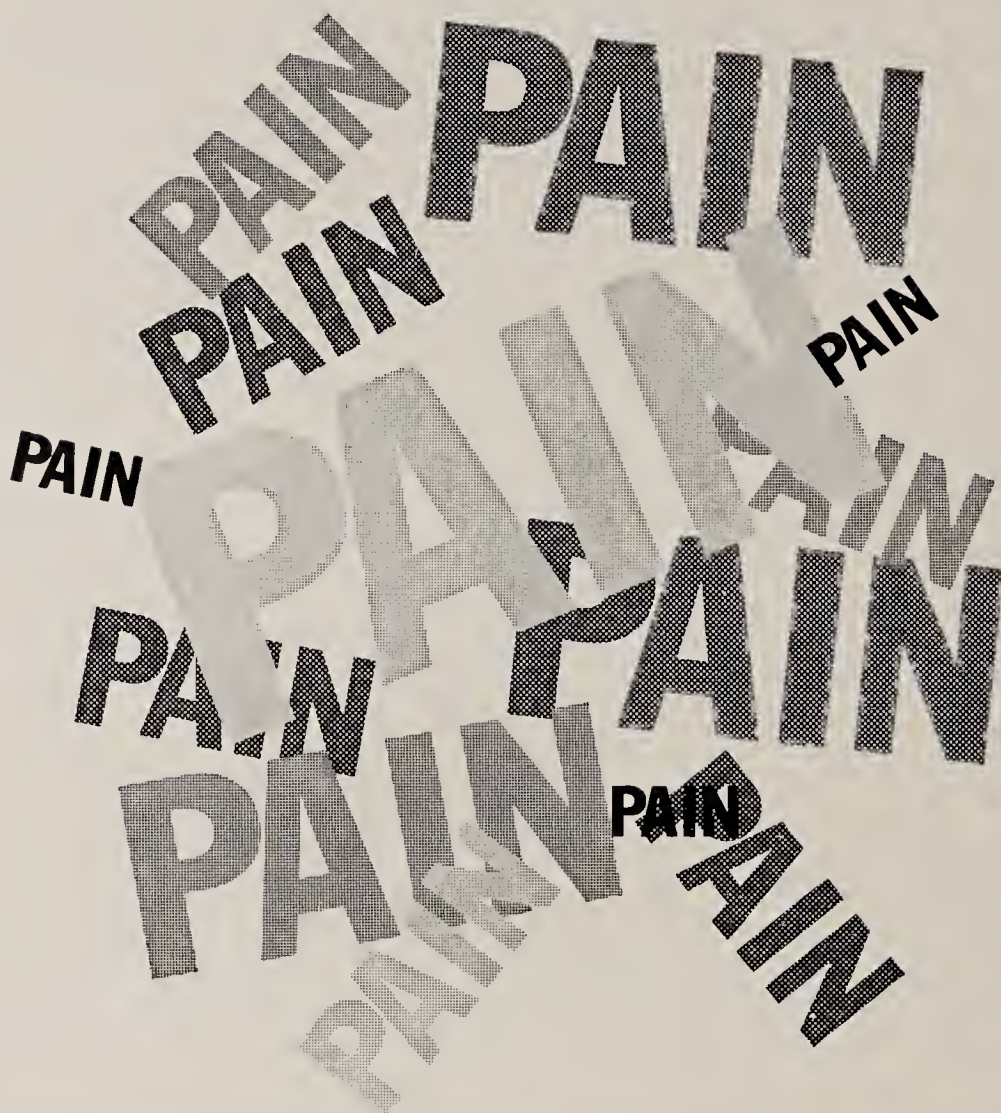
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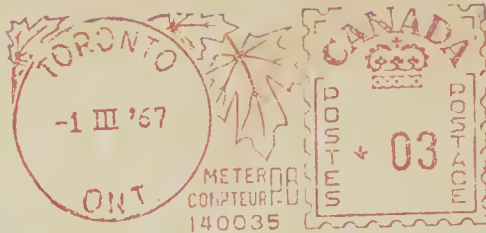
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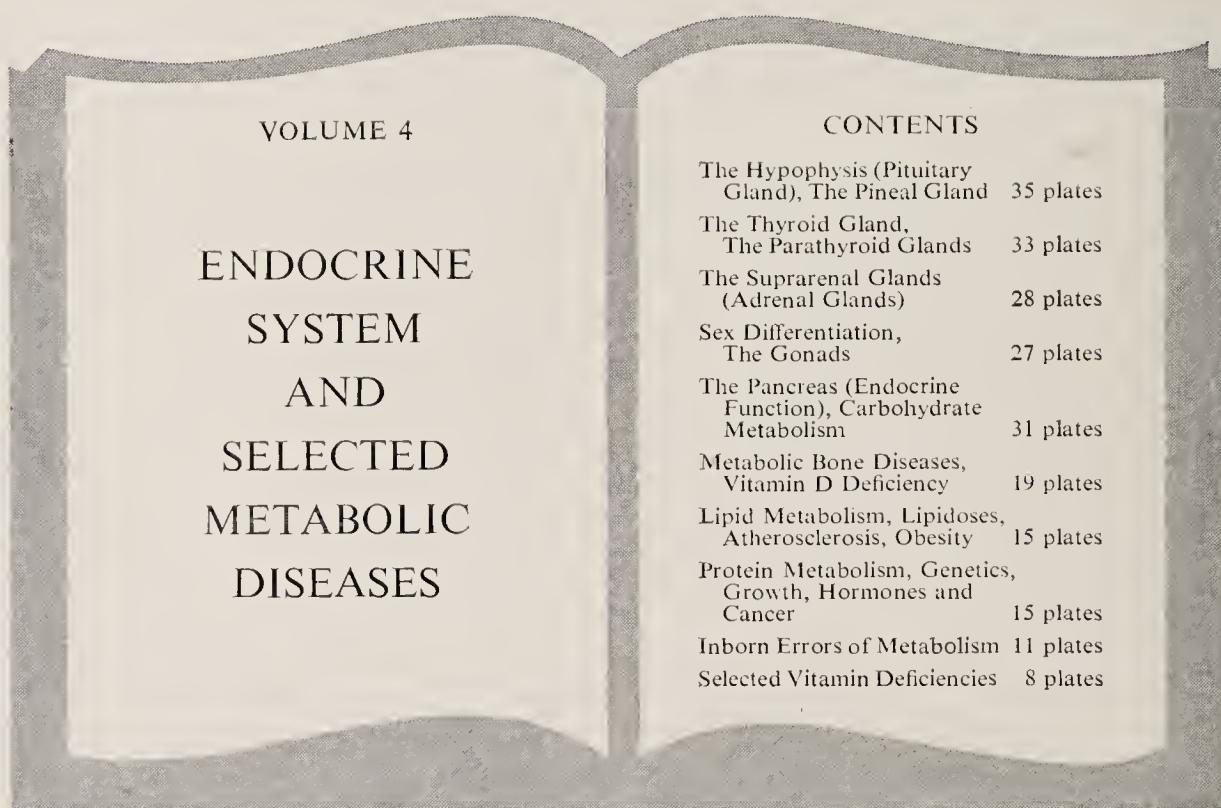
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